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REVIEW ARTICLE

EAACI IG Biologicals task force paper on the use of biologic agents in allergic disorders

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Abstract

Biologic agents (also termed biologicals or biologics) are therapeutics that are synthesized by living organisms and directed against a specific determinant, for example, a cytokine or receptor. In inflammatory and autoimmune diseases, biologicals have revolutionized the treatment of several immune-mediated disorders. Biologicals have also been tested in allergic disorders. These include agents targeting IgE; T helper 2 (Th2)-type and Th2-promoting cytokines, including interleukin-4 (IL-4), IL-5, IL-9, IL-13, IL-31, and thymic stromal lymphopoietin (TSLP); pro-inflammatory cytokines, such as IL-1β, IL-12, IL-17A, IL-17F, IL-23, and tumor necrosis factor (TNF); chemokine receptor CCR4; and lymphocyte surface and adhesion molecules, including CD2, CD11a, CD20, CD25, CD52, and OX40 ligand. In this task force paper of the Interest Group on Biologicals of the European Academy of Allergy and Clinical Immunology, we review biologicals that are currently available or tested for the use in various allergic and urticarial pathologies, by providing an overview on their state of development, area of use, adverse events, and future research directions.

Abbreviations
ABPA, allergic bronchopulmonary aspergillosis; ACQ-5/ACQ-6/ACQ-7, 5-item/6-item/7-item ACQ; ACQ, asthma control questionnaire; ADA, antidrug antibody; AD, atopic dermatitis; AE, adverse event; BHR, bronchial hyper-responsiveness; CAU, chronic autoimmune urticaria; CindU, chronic inducible urticaria; CSU, chronic spontaneous urticaria; DC, dendritic cell; EGPA, eosinophilic granulomatosis with polyangiitis; EoE, eosinophilic esophagitis; FeNO, exhaled nitric oxide; FEV1, forced expiratory volume in one second; HES, hypereosinophilic syndromes; ICS, inhaled corticosteroid; ILC, innate lymphoid cell; IL, interleukin; IM, intramuscular; IV, intravenous; LABA, long-acting beta-agonist; mAb, monoclonal antibody; NKT, natural killer T cell; NP, nasal polyposis; OIT, oral immunotherapy; PEF, peak expiratory flow; QoL, quality of life; RCT, randomized controlled trial; RIT, rush immunotherapy; SAE, serious adverse event; SAR, seasonal allergic rhinitis; SC, subcutaneous; SIT, specific immunotherapy; Th, T helper; TNF, tumor necrosis factor (also known as TNF-α); TSLP, thymic stromal lymphopoietin; VIT, venom-specific immunotherapy.

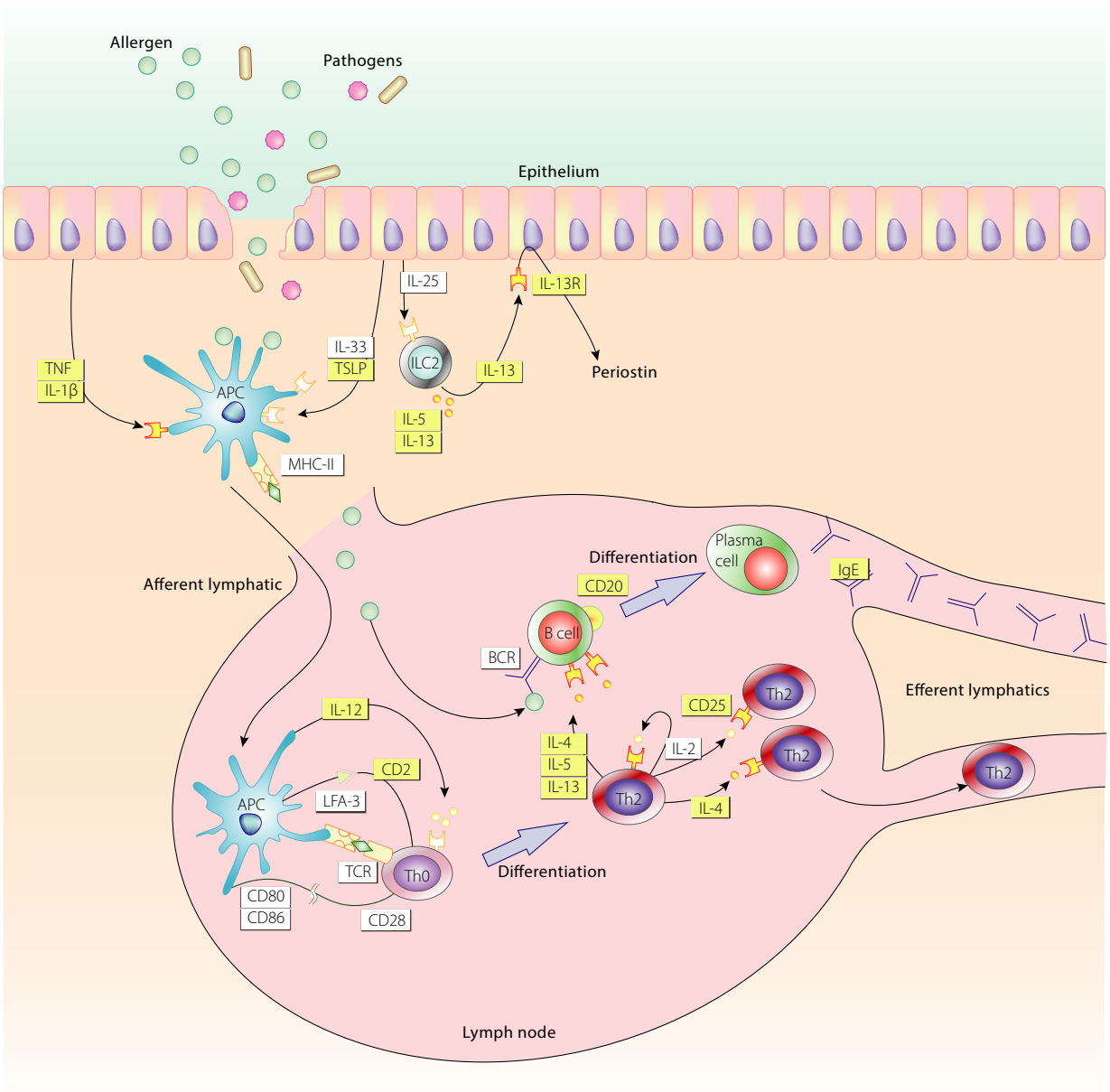

Figure 1 The sensitization phase of an allergic reaction. An allergic reaction requires the priming (or sensitization) of an individual to an allergen. Allergens enter via microlesions of a body surface (such as the skin or the lungs), and their entry might be accompanied by a concomitant exposure to pathogens. The allergen is phagocytosed by antigen-presenting cells (APC), which subsequently mature, aided by stimulation with different cytokines produced by activated epithelial cells, such as tumor necrosis factor (TNF), IL-1β, IL-33, and thymic stromal lymphopoietin (TSLP), as well as contact with microbial products. Early on, also type-2 innate lymphoid cells (ILC2) become activated by IL-25 among other factors, and produce IL-5 and IL-13, the latter of which can act on epithelial cells. Mature APCs migrate to the local draining lymph nodes where they stimulate undifferentiated $CD4^+$ T helper (Th0) cells via interaction of major histocompatibility complex (MHC) class II/allergen fragment–T-cell receptor (TCR), CD80/CD86–CD28, and lymphocyte function-associated antigen 3 (LFA-3)–CD2, as well as cytokines, including IL-12. Under the influence of these interactions and stimuli, Th0 cells differentiate to Th2 cells, producing the Th2-type cytokines IL-4 and IL-13 and further expanding via auto- and paracrine actions of IL-2 binding to CD25 along with IL-2 receptor βγ. In parallel, allergen-specific B cells become activated via their B-cell receptor (BCR) by the allergen, leading to their differentiation and, under the influence of Th2-type cytokines, isotype class switching to IgE-producing plasma cells. During this process, B cells lose their surface CD20 expression. The molecules highlighted in yellow indicate the targets of biologicals for allergic disorders.

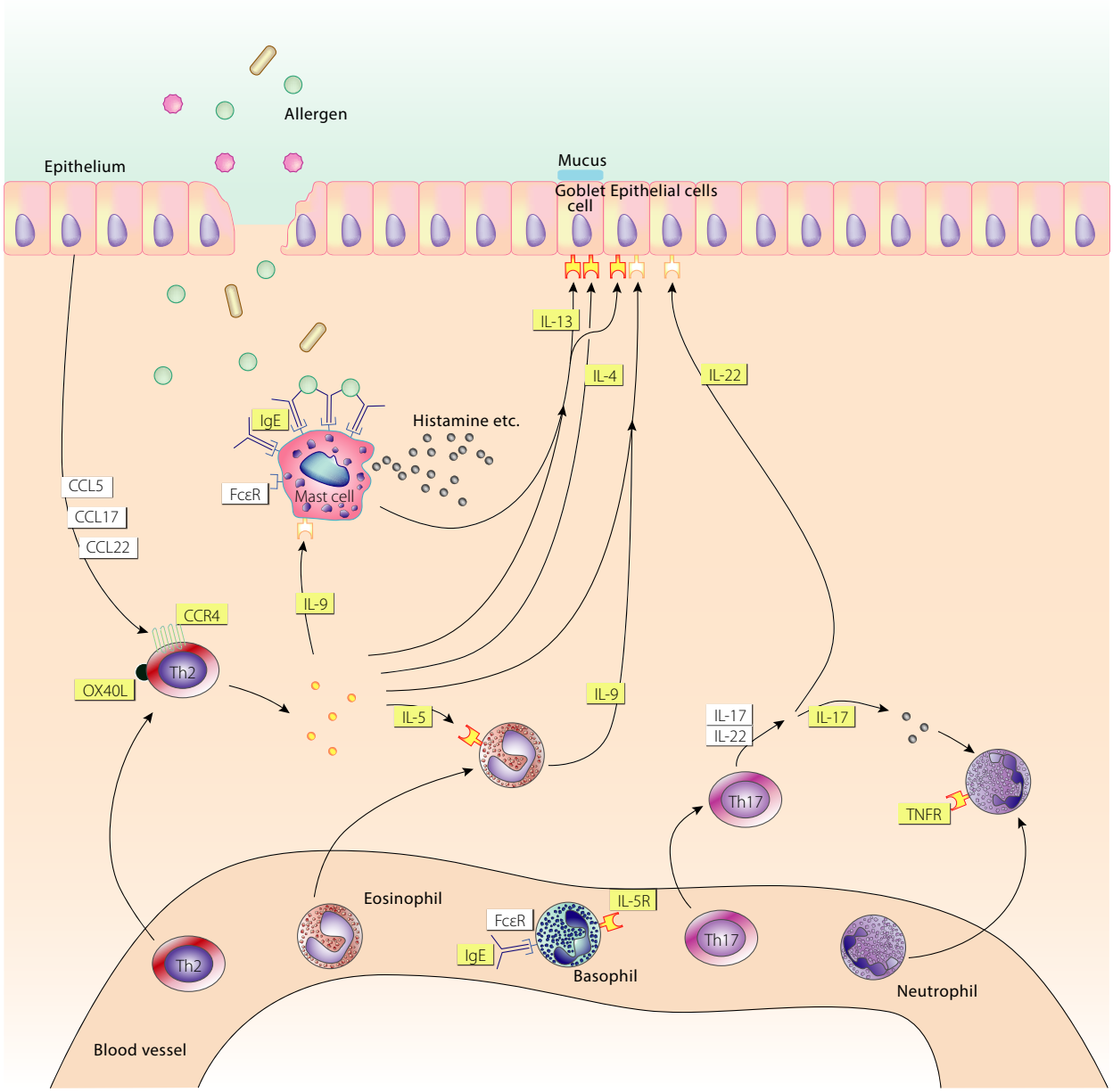

Figure 2 The re-exposure and chronic relapsing phase of an allergic reaction. In an individual sensitized to an allergen (see Fig. 1), the allergen-specific IgE molecules produced by B cells and plasma cells have bound, via Fcε receptors FcεRI and FcεRII, to mast cells and basophils. Upon re-exposure to the same allergen, allergen molecules bind to these IgE molecules, thereby cross-linking and activating FcεRs on mast cells and basophils and leading to the release within minutes of various mediators, such as histamine, leukotrienes, prostaglandins, tryptase, heparin, serotonin, and proteases. Similar to the arming of mast cells by IgE following sensitization, also T helper 2 (Th2) cells become recruited to peripheral sites via activation of specific chemokine receptors such as CCR4 by chemokines produced in these tissues, including CCL5, CCL17, and CCL22 in the skin. Th2 cells, upon activation by their T-cell receptor or cytokines, secrete Th2-type cytokines, including IL-4, IL-5, IL-9, and IL-13, which synergize with other sources of these cytokines to stimulate immune, epithelial, and airway goblet cells (the latter producing mucus in the airways). Chronification of certain allergic disorders is paralleled by a recruitment of Th17 cells, able to produce IL-17 and IL-22, which stimulate neutrophils and epithelial cells, respectively. Neutrophils can also be stimulated by various other cytokines, including TNF. The molecules highlighted in yellow indicate the targets of biologicals for allergic disorders.

Biologic agents (biologicals) are usually large molecular-weight therapeutics, such as monoclonal antibodies (mAb), that are synthesized by living organisms. In contrast to chemical compounds and small-molecule agonists or antagonists, biologicals bind a specific determinant, for example, a cytokine or receptor. Owing to this selectivity, biologicals are ideal for 'personalized' or 'precision' medicine. This, however, requires detailed knowledge of the pathophysiology and subtypes (also termed endotypes) of the disease in question, a challenge that also applies to allergic and urticarial disorders (1). Below, we will briefly discuss the prevalent mechanisms of allergic reactions, which will be helpful in understanding the herein discussed biologicals.

Allergic disorders are caused by an immune response to an innocuous environmental antigen, termed the allergen. Such allergic reactions usually require the sensitization of an individual to an allergen during a first contact (Fig. 1), followed by a hypersensitivity reaction upon subsequent exposure to the same allergen (Fig. 2). The molecular similarity of allergenic epitopes of two different allergens can lead to cross-reactivity, a situation where sensitization toward an allergen can cause a hypersensitivity reaction toward another allergen, as seen, for example, with the oral allergy syndrome against apple in birch pollen-sensitized individuals.

Allergic reactions are typically characterized by the emergence of T helper (Th) 2-type cytokines, including interleukin-4 (IL-4), IL-5, IL-9, IL-13, IL-25, and IL-31, which favor antibody isotype class switching to immunoglobulin E (IgE), along with the presence of eosinophil granulocytes (eosinophils), basophil granulocytes (basophils), and mast cells (2, 3) (Figs 1 and 2). Notably, initial IL-4 production by T cells, basophils, and natural killer T (NKT) cells appears to be important for Th2 responses, although recent data have shown that the IL-1 family member IL-33 can promote Th2-type differentiation. Furthermore, production of thymic stromal lymphopoietin (TSLP) by epithelial cells can also induce Th2-type inflammation via polarizing dendritic cells (DC). However, certain endotypes of allergic asthma and other allergic pathologies can feature another type of cytokine milieu, more reminiscent of Th1- or Th17-type diseases, with the presence of type-I interferons, IL-17-producing T cells, and abundant neutrophil granulocytes (neutrophils) (1).

Once IgE is produced by B cells during the sensitization phase to an allergen, IgE binds to Fcε receptors FcεRI and FcεRII on mast cells and basophils (4) (Fig. 2), thus arming these cells for subsequent contact with the same or a structurally related allergen. Allergic inflammation is characterized by an early-phase response and a late-phase response. During the early-phase reaction, mast cells and basophils covered with allergen-specific IgEs become activated and release within minutes various mediators, such as histamine, leukotrienes, prostaglandins, tryptase, heparin, serotonin, and proteases (5). The early phase is dependent on the induction of IgE cross-linking on effector cells by conformational and/or linear allergenic epitopes, while the late-phase response can be triggered independently of IgE by linear peptides being recognized by specific T cells. Mast cell-released vasoactive factors along with allergen presentation lead to the late-phase allergic response, which is characterized by increased vasopermeability and infiltration and recruitment of additional granulocytes, T cells, and other immune cells. Upon local activation of T cells, production of Th2-type cytokines, chemokines, and growth factors results in further immune activation including the stimulation of eosinophils by IL-5 and mast cells by IL-9 (Fig. 2). IL-4, IL-9, IL-13, and IL-31 exert diverse actions on macrophages, turning them into alternatively activated (also termed M2) macrophages, and on lung epithelial and smooth muscle cells, thereby contributing to mucus production, airway goblet cell hyperplasia, airway hyper-responsiveness, myofibroblast differentiation, contractility of smooth muscle cells, extracellular matrix deposition, and itch sensation (2, 3, 5). IL-4, IL-9, and IL-25 play important roles in the polarization and activation of Th2 cells, while IL-25 can also act on type-2 innate lymphoid cells (ILC), which, based on preclinical data, might play a role in allergic responses. Th2-type cytokines exert their actions by binding to specific receptors, which can be targeted by specific biologicals (summarized in Table 1), as outlined below.

IgE-producing B cells can be targeted either by anti-IgE or by anti-CD20 mAbs. IgE-directed strategies include the anti-IgE mAbs omalizumab, MEDI4212, and QGE031, as well as quilizumab, a humanized mAb targeting the extracellular segment (also called M1 prime or M1') of membrane IgE (6). Omalizumab leads not only to a reduction in IgE molecules but also to decreased FcεR1 expression on basophils, mast cells, and cutaneous DCs (7). The target of rituximab, CD20, is expressed at high levels on immature and mature B cells, including memory B cells, whereas plasmablasts and plasma cells lose their CD20 expression and are thus resistant to anti-CD20 treatment (8).

IL-4 is produced by T cells, basophils, and NKT cells. IL-4 signaling is mediated by binding of IL-4 to its receptors, consisting of heterodimers made of IL-4Rα and common γ-chain (γ_c, also termed CD132) or IL-4Rα plus IL-13Rα1. IL-4Rα is mainly expressed on $CD4^+$ and $CD8^+$ T cells, B cells, macrophages, lung epithelial cells, airway goblet cells, and smooth muscle cells. However, other tissue cells have also been described to respond to IL-4, such as cells of the liver blood system, placenta, and brain. A key role of IL-4 is the polarization and maintenance of Th2 cells (5). Biologicals directed against IL-4Rα include AMG-317, dupilumab, and pitrakinra. While AMG-317 and dupilumab are both mAbs targeting IL-4Rα, pitrakinra is a recombinant mutated IL-4 molecule (IL-4 mutein) that binds to IL-4Rα without causing a signal, thus competing with normal endogenous IL-4 and IL-13 (see below). Altrakincept is a recombinant soluble form of the extracellular part of IL-4Rα, able to capture soluble IL-4, thus preventing binding to IL-4Rs. A somewhat similar effect is achieved by pascolizumab and VAK694, both neutralizing anti-IL-4 mAbs.

IL-5 is secreted mainly by Th2 cells, mast cells, NKT cells, basophils, eosinophils, and type-2 ILCs. The IL-5R is a heterodimer composed of α- and β-subunits, with IL-5Rα responsible for binding of IL-5 and IL-5Rβ necessary for signaling. IL-5Rα is expressed both on progenitors of and mature eosinophils and basophils, and on B cells. IL-5

Table 1 Overview of biologicals used for allergic and urticarial disorders. The biologicals are ordered alphabetically according to their target antigen, followed by drug name

Target antigen	Drug name (alternative or brand name)	Structure	Route	Dosing	$T_{1/2}$
CCR4	Mogamulizumab (KW0761, AMG-761, Poteligeo®)	mAb (IgG1κ)	IV	–	18–21 d
CD2	Alefacept (Amevive®)	LFA-3-IgG1 Fc fusion protein	IM	15 mg weekly for 12 wk	11 d
CD11a	Efalizumab (Raptiva®)	mAb (IgG1κ)	SC	1 mg/kg weekly	5 d
CD20	Rituximab (Rituximab®, Rituxan®)	mAb (IgG1κ)	IV	4 times 375 mg/m^2 or twice 1 mg/kg	22 d
CD25	Daclizumab (Zenapax®)	mAb (IgG1)	IV	1 mg/kg	20 d
CD52	Alemtuzumab (Campath®)	mAb (IgG1κ)	SC or IV	5–30 mg 1–3 times weekly	12 d
IgE	MEDI4212	mAb (IgG1)	SC	–	–
IgE	Omalizumab (Xolair®, Xolairoid®)	mAb (IgG1)	SC	75–600 mg q 2 or 4 wk	26 d
IgE	QGE031	mAb (IgG1κ)	SC	–	–
IgE, M1′ segment	Quilizumab (MEMP1972A, RG7449)	mAb (IgG1κ)	SC or IV	3–5 mg/kg q 4 wk	20–21 d
IL-1β	Canakinumab (Ilaris®)	mAb (IgG1κ)	SC	150 mg monthly	26 d
IL-1β	Rilonacept (Arcalyst®)	Dimeric fusion protein	SC	320 mg weekly	8.6 d
IL-1R1	Anakinra (Kineret®)	Recombinant IL-1Ra	SC	100 mg daily	4–6 h
IL-4	Altrakincept	Recombinant IL-4Rα	Inhaled	3 mg	7 d
IL-4	Pascolizumab (SB 240683)	mAb (IgG1)	SC or inhaled	–	9 d
IL-4	VAK694	mAb	IV	3 mg/kg q 4 wk	–
IL-4Rα	AMG-317	mAb (IgG2a)	SC or IV	75–300 mg weekly	3.4 d
IL-4Rα	Dupilumab (SAR2311893, REGN668)	mAb (IgG4)	SC	300 mg weekly	–
IL-4Rα	Pitrakinra (Aerovant™)	IL-4 mutein (mutations: R121D, Y124D)	Inhaled	60 mg twice daily	0.5–0.6 h
IL-4/IL-13	QBX258 (combination of VAK694 and QAX576)	mAbs targeting IL-4 (VAK694) and IL-13 (QAX576)	IV	–	–
IL-5	Mepolizumab (SB 240563, Bosatria®)	mAb (IgG1κ)	IV	750 mg monthly	21 d
IL-5	Reslizumab (SCH55700)	mAb (IgG4)	IV	1–3 mg/kg q 4 wk	25–30 d
IL-5Rα	Benralizumab (MEDI-563)	mAb (IgG1)	SC or IV	25–200 mg 1–3 times monthly	18 d
IL-9	Enokizumab (MEDI-528)	mAb	SC or IV	0.3–3.0 mg/kg or 50 mg twice weekly	35–38 d
IL-12p40 and IL-23p40	Ustekinumab (Stelara®)	mAb (IgG1κ)	SC	45 mg q 12 wk	21 d
IL-13	ABT-308	mAb	SC or IV	–	–
IL-13	Anrukinzumab (IMA-638)	mAb (IgG1κ)	SC	2 mg/kg weekly	25 d
IL-13	CNTO-5825	mAb (IgG1κ)	SC or IV	0.1–10 mg/kg IV or 3 mg/kg SC	22–32 d
IL-13	GSK679586	mAb (IgG1)	IV	10 mg/kg 3 times monthly	21 d
IL-13	Lebrikizumab (MILR1444A)	mAb (IgG4κ)	SC	250 mg monthly	–
IL-13	IMA-026	mAb (IgG1κ)	SC	2 mg/kg weekly	26 d
IL-13	QAX576	mAb (IgG1κ)	IV	6 mg/kg every 3 or 4 wk	–
IL-13	Tralokinumab (CAT-354)	mAb (IgG4λ)	SC	150–600 mg q 2 wk	14–21 d
IL-17A	Secukinumab (Cosentyx®)	mAb (IgG1κ)	SC or IV	150–300 mg q 4 wk	28 d
IL-17RA	Brodalumab	mAb (IgG2)	SC or IV	SC: 70–280 mg q 2 wk IV: 420–700 mg q 4 wk	–
IL-22	ILV-094	mAb	SC or IV	–	–
IL-31	BMS-981164	mAb	SC	–	–
IL-31R	CIM331	mAb	SC	–	–
OX40L (CD252)	huMAb OX40L	mAb (IgG1)	IV	4 mg/kg monthly	28.5 d
TNF	Adalimumab (Humira®)	mAb (IgG1κ)	SC	40 mg q 2 wk	15 d

Table 1 (continued)

Target antigen	Drug name (alternative or brand name)	Structure	Route	Dosing	$T_{1/2}$
TNF	Golimumab (Simponi®)	mAb (IgG1κ)	SC	50 mg monthly	14 d
TNF	Infliximab (Remicade®)	mAb (IgG1κ)	IV	3–5 mg/kg q 6–8 wk	7–10 d
TNF + LT-β	Etanercept (Enbrel®)	TNFR-IgG1-Fc fusion protein	SC	25 mg twice or 50 mg once weekly	4 d
TSLP	AMG-157	mAb (IgG2λ)	IV	700 mg 3 times monthly	–

d, day(s); LFA-3, lymphocyte function-associated antigen 3; LT, lymphotoxin; h, hour(s); IM, intramuscular; IV, intravenous; mAb, monoclonal antibody; SC, subcutaneous; OX40L, OX40 ligand; q, each / every; TNF, tumor necrosis factor; TSLP, thymic stromal lymphopoietin; wk, week(s).

induces the maturation, activation, and recruitment of eosinophils. Biologicals interfering with IL-5 and its receptor comprise benralizumab, an anti-IL-5Rα mAb, as well as mepolizumab and reslizumab, two anti-IL-5 mAbs. Unlike mepolizumab and reslizumab, benralizumab targets IL-5Rα and might thus also affect leukocytes expressing low levels of IL-5Rα via antibody-dependent cell-mediated cytotoxicity.

IL-9 is produced by Th2 cells, Th9 cells, basophils, eosinophils, mast cells, and maybe neutrophils (2). IL-9 mediates its action by binding to IL-9Rα and γ_c. IL-9 enables the development and attraction of mast cells, and plays important roles in the polarization and activation of Th2 cells. Together with IL-4 and IL-13, IL-9 acts on lung epithelial and smooth muscle cells, thus contributing to airway hyper-responsiveness (5). Enokizumab is an IL-9-targeting mAb.

IL-13 is predominantly synthesized by Th2 cells, NKT cells, mast cells, basophils, and type-2 ILCs (2). IL-4Rα–IL-13Rα1 heterodimers serve as a high-affinity receptor of IL-13, whereas IL-13 can bind with low affinity to IL-13Rα1 only. Moreover, IL-13 interacts with high affinity with IL-13Rα2, which lacks signaling capacity, thus inhibiting the action of IL-13. IL-13Rα1 is present on B cells, eosinophils, monocytes, macrophages, lung epithelial cells, airway goblet cells, endothelial cells, and smooth muscle cells. Along with IL-4, IL-13 is responsible for the generation of alternatively activated macrophages and for activating B cells to produce IgE. IL-13 also causes mucus production, goblet cell hyperplasia, airway hyper-responsiveness, myofibroblast differentiation, contractility of smooth muscle cells, and airway remodeling. The latter is believed to rely, among others, on the IL-13-mediated periostin secretion by bronchial epithelial cells, with periostin exerting paracrine effects on fibroblasts leading to airway remodeling (9), perhaps explaining the role of IL-13 in corticosteroid-resistant asthma (10). IL-13-targeting biologicals encompass several anti-IL-13 mAbs, including ABT-308, anrukinzumab, IMA-026, lebrikizumab, CNTO-5825, GSK679586, QAX576, and tralokinumab.

IL-12 and IL-23 are secreted by activated monocytes, macrophages, and DCs (11). Both cytokines consist of two subunits, of which they share the p40 subunit, while IL-12 also contains a p35 and IL-23 a p19 subunit. IL-12 binds to the IL-12R comprised of IL-12Rβ1 and IL-12Rβ2, whereas specific binding to IL-23 is conferred by IL-23R, which together with IL-12Rβ1 forms the signaling receptor of IL-23. Functional IL-12Rs and IL-23Rs are found on macrophages, DCs, natural killer (NK) cells, and activated T cells. Accordingly, IL-12 and IL-23 stimulate these cells and affect T-cell polarization and effector functions. Moreover, both cytokines appear to influence B-cell responses, either directly (IL-12) or indirectly (both IL-12 and IL-23). Ustekinumab is a mAb targeting the p40 subunit of IL-12 and IL-23.

Apart from IL-25, which is also known as IL-17E, other members of the IL-17 family might play a role in certain endotypes of allergic disorders, such as allergic asthma and atopic dermatitis (AD). IL-17A (also termed IL-17) and IL-17F are produced by Th17 cells, $CD8^+$ T cells, γδ T cells, NK cells, NKT cells, and type-3 ILCs. IL-17A and IL-17F exist either as IL-17A-IL-17A and IL-17F-IL-17F homodimers, respectively, or as IL-17A-IL-17F heterodimers. All three dimers bind to receptor multimers composed of IL-17RA and IL-17RC (12). IL-17RA is found on endothelial cells, epithelial cells, keratinocytes, synoviocytes, fibroblasts, bone marrow stromal cells, myeloid cells, and B and T cells (12). Activation of these cells by IL-17A and IL-17F leads to the secretion of pro-inflammatory and chemotactic factors, including IL-1β, IL-6, tumor necrosis factor (TNF; also termed TNF-α), and CXCL8 (also known as IL-8). Biologicals directed against IL-17A or its receptor are brodalumab, a mAb targeting IL-17RA, and secukinumab, an anti-IL-17 mAb.

Th17, Th22, NK cells, and mast cells are able to produce IL-22. IL-22 binds to a heterodimer consisting of IL-10R2 and IL-22R1, the latter present on keratinocytes, hepatocytes, and airway and intestinal epithelial cells. ILV-094 is a mAb targeting IL-22.

In addition to the above-mentioned Th2- and Th17-type mediators, several other cytokines have been implicated in the initiation, maintenance, and chronification of allergic responses, including IL-1 family members (such as IL-1β and IL-33), IL-31 (causing pruritus), and TNF, as well as adhesion and activation molecules of activated T and B cells (such as CD2, CD11a, CD25, and CD52), which have been targeted in different allergic conditions using biologicals. IL-1β can be inhibited using a recombinant IL-1R antagonist (IL-1Ra; anakinra), an anti-IL-1β mAb (canakinumab), or an IL-1 trap (rilonacept), the latter consisting of the extracellular domains of IL-1R1 and IL-1R accessory protein linked to human IgG1-Fc. BMS-981164 and CIM331 are mAbs targeting IL-31 and IL-31R, respectively. TNF inhibitors, such

Table 2 Overview of biologicals and their current stages of development for the indicated allergic and urticarial disorders

Target	Biological	Asthma	Allergic rhinitis	ABPA	Urticaria	Atopic dermatitis	Food allergy	Eosinophilic disorders
CCR4	Mogamulizumab	(2)						
CD2	Alefacept					CR		
CD20	Rituximab				1/2	CR		
CD25	Daclizumab	2						
CD52	Alemtuzumab							CR
IgE	MEDI4212	1	1			1		
IgE	Omalizumab	FDA, EMA	2	4	3/4	4	2	EGPA: CR NP: 2
IgE	QGE031	1/2				2		
IgE, M1′ segment	Quilizumab	2	1		2			
IL-1β	Canakinumab				2			
IL-1β	Rilonacept				2			
IL-1R1	Anakinra					1		
IL-4	Altrakincept	2 (halted)						
IL-4	Pascolizumab	1 (halted)						
IL-4	VAK694	1	2					
IL-4Rα	AMG-317	2				1		
IL-4Rα	Dupilumab	2a	2			2, (3)		NP: 2
IL-4Rα	Pitrakinra	2b				2		
IL-4/IL-13	QBX258	1, (2)						
IL-5	Mepolizumab	2, (3)	2			2, (3)		EGPA: 2 EoE: 2 HES: 3 NP: 1/2
IL-5	Reslizumab	3						EoE: 3 HES 2 NP: 1/2
IL-5Rα	Benralizumab	1, (3)						
IL-9	Enokizumab	2b						
IL-12p40 and IL-23p40	Ustekinumab					2		
IL-13	ABT-308	1						
IL-13	Anrukinzumab	2						
IL-13	CNTO-5825	1						
IL-13	GSK679586	2						
IL-13	Lebrikizumab	2, (3)						
IL-13	IMA-026	1						
IL-13	QAX576	2	2					2
IL-13	Tralokinumab	2a, (2b)						
IL-17A	Secukinumab	2						
IL-17RA	Brodalumab	2						
IL-22	ILV-094					2		
IL-31	BMS-981164					1		
IL-31R	CIM331					2		
OX40L	huMAb OX40L	2	1					
TNF	Adalimumab				CR			
TNF	Golimumab	2 (susp)						
TNF	Infliximab	2			CR	CR		
TNF + LT-β	Etanercept	2			CR	CR		
TSLP	AMG-157	1b, (2)				1		

ABPA, allergic bronchopulmonary aspergillosis; CR, case report(s); EGPA, eosinophilic granulomatosis with polyangiitis; EMA, European Medicines Agency; EoE, eosinophilic esophagitis; halted, development halted; FDA, U.S. Food and Drug Administration; HES, hypereosinophilic syndromes; LT, lymphotoxin; NP, nasal polyposis; Schnitzler, Schnitzler's syndrome; susp, suspended.
Numbers refer to the most advanced developmental phase that has been completed to date, while numbers in parentheses indicate phases that are recruiting or ongoing. Color coding: red, CR; yellow, phase 1; blue, phase 2; green, phase 3 and higher (up to approval).

as anti-TNF mAbs (adalimumab, golimumab, infliximab) and TNFR-IgG1-Fc fusion protein (etanercept), have been extensively used in other immunological disorders and also tried in allergic conditions. Alefacept is a fusion protein of lymphocyte function-associated antigen-3 (LFA-3, also termed CD58) linked to IgG1-Fc, thus binding CD2. Different mAbs targeting CD11a, CD25, and CD52 are efalizumab, daclizumab, and alemtuzumab, respectively.

The chemokine receptor CCR4 (also called CD194) is expressed on memory $CD4^+$ T cells, especially skin-homing T cells, possibly $CD4^+$ regulatory T cells, and platelets. CCR4 mediates the recruitment of these cells toward a range of chemokines, including CCL2 (MCP-1), CCL4 (MIP-1), CCL5 (RANTES), CCL17 (TARC), and CCL22 (MDC). Mogamulizumab is a mAb targeting CCR4.

The following parts of this article discuss in detail the current state of experience and development of the before-mentioned biologicals in different allergic and urticarial diseases (summarized in Table 2), followed by their use in specific immunotherapy (SIT), their adverse events (AE), and future research directions in this field. Although allergen extracts, recombinant native or modified allergens, and allergen fragments might also qualify as biological response modifiers according to our definition, we will not discuss allergens but focus this article on the before-mentioned biologicals.

Diseases

Asthma

CCR4: Mogamulizumab (phase 1 completed)
Mogamulizumab is approved in Japan for the treatment of refractory or relapsed $CCR4^+$ T-cell leukemia/lymphoma (13). Currently, a phase-1 randomized controlled trial (RCT) investigating the safety, tolerability, pharmacokinetics, and pharmacodynamics of mogamulizumab in patients with asthma has been terminated, but, so far, no results have been published (13, 14).

CD25: Daclizumab (phase 2 completed)
A phase-2 RCT (n = 115) in patients with moderate-to-severe persistent asthma has been completed (15), the primary endpoint being the forced expiratory volume in one-second (FEV1) and secondary endpoints consisting of asthma exacerbations, peak expiratory flow (PEF), use of rescue medication, and asthma symptoms. Daclizumab-treated patients showed a slight improvement in FEV1, reduced asthma symptoms, and reduced use of rescue medications. Also, daclizumab reduced the frequency of asthma exacerbations (15).

Conclusion – Further studies are needed to assess the possible use of daclizumab in patients with asthma. In Europe, daclizumab has been withdrawn from the market in 2008 upon request of the marketing authorization holder for commercial reasons. This decision was not related to any safety concerns (16).

IgE: MEDI4212 (phase 1 completed)
The results of a phase-1 RCT assessing safety and tolerability (primary endpoints) of MEDI4212 in allergic patients (asthma, rhinitis, AD) have not become available yet (17). Secondary endpoints included pharmacokinetics, immunogenicity, and pharmacodynamics.

IgE: Omalizumab (approved)
Several RCTs have shown that omalizumab decreases the use of inhaled corticosteroids (ICS) and rescue medication, reduces the frequency of exacerbations, emergency visits, and hospitalizations, and improves asthma-related quality of life (QoL) in patients with severe asthma not otherwise manageable and in (inner city) children with asthma (18–21). Although there is some evidence that omalizumab reduces airway remodeling and improves FEV1, these findings need further confirmation (20, 22).

The efficacy of omalizumab has also been shown in real-life settings in multicenter observational studies (23, 24). Moreover, omalizumab has been used in nonallergic (intrinsic) asthma associated with nasal polyposis (NP), showing a reduction in the frequency of exacerbations (25). However, further studies are needed to confirm these preliminary results.

Omalizumab is currently approved for the use in patients aged 6 years and above with positive skin test or *in vitro* reactivity to a perennial aeroallergen who suffer from moderate-to-severe (US guidelines) or severe (European guidelines) persistent asthma despite the use of high-dose ICS (≥800 μg/day beclomethasone dipropionate or equivalent) plus long-acting beta-agonist (LABA) and/or other controllers (4, 26). Persistent asthma manifestations include reduced lung function and frequent daytime symptoms or nighttime awakenings (4). Further data are needed to determine the optimum duration of treatment (24).

Omalizumab is well tolerated and considered cost-effective compared to standard therapy alone (27).

Conclusion – Omalizumab is indicated in patients with moderate-to-severe persistent asthma despite the use of high-dose ICS plus LABA and/or other controller medications (4, 26).

IgE: Omalizumab and specific immunotherapy
A multicenter RCT investigated the combination of omalizumab (given 16 weeks prior to and throughout the first 3 weeks of SIT) together with cluster SIT for 1–3 different perennial allergens (dog or cat dander or house dust mite) in asthmatic patients (n = 248). Omalizumab-treated patients had fewer respiratory AEs and significantly lower rates of seasonal allergic rhinitis (SAR). Moreover, the number of patients that reached the maintenance dose was higher in the group receiving omalizumab (28).

Compared to SIT alone, the addition of omalizumab also improved the efficacy of SIT on symptoms and reduced the risk of systemic reactions by SIT (21, 29), as shown in a parallel-group RCT in children with allergic rhinitis (n = 221) and a double-blind multicenter RCT (n = 140) in adults with moderate persistent uncontrolled asthma receiving ICS. However, it is unclear whether these effects persist once omalizumab is discontinued, while maintaining SIT for a total of 3–5 years (30). In rush immunotherapy (RIT), omalizumab

was used as a premedication due to its ability to prevent serious AEs (SAE) following immunotherapy (31) (see section 'Allergic rhinitis').

IgE: QGE031 (phase 1/2 completed, phase 2 ongoing)
A phase-1 and a phase-1/2 study for the use of QGE031 in patients with asthma completed investigating the efficacy (compared to omalizumab and placebo), safety, tolerability, pharmacokinetics, pharmacodynamics, and immunogenicity, but the results have not become available yet (32, 33). Furthermore, two phase-2 studies are currently ongoing, investigating dosing and long-term safety (34, 35).

IgE: Quilizumab (phase 2 completed, phase 2b ongoing)
A phase-2 RCT in patients ($n = 29$) with mild asthma evaluated efficacy, safety, and tolerability of quilizumab, given three times intravenous (IV) 4 weeks apart, followed by an allergen challenge on day 86 (6). Primary endpoint was the late asthmatic response. Quilizumab showed a significant decrease in total and allergen-specific serum IgE levels as well as a reduction in the early asthmatic response. Remarkably, the reduction in IgE remained for at least 6 months after the last dose of quilizumab. Furthermore, following quilizumab, late asthmatic response and sputum and blood eosinophils were diminished although these changes remained nonsignificant.

Conclusion – The results of quilizumab in asthma are promising. Currently, a phase-2b trial in patients with persistent asthma is ongoing (36).

IL-4: Altrakincept (phase 2 completed, development halted)
In a double-blind, placebo-controlled phase-1/2 RCT using altrakincept, 25 patients with moderate asthma requiring ICS were randomly assigned to receive either a single inhalation of altrakincept 1500 μg or altrakincept 500 μg, or placebo after stopping ICS. Treatment with altrakincept produced significant improvement in FEV1 and forced expiratory flow at 25–75% of forced vital capacity compared to placebo. Asthma symptom scores stabilized, and patients required significantly less β2-agonist treatment when receiving altrakincept. The study concluded that 1500 μg altrakincept was as safe as and significantly more effective than 500 μg altrakincept (37).

A second study ($n = 62$) that was conducted suffered from considerable withdrawal of patients as prior to starting the study ICS were discontinued, leading to a worsening of asthma symptoms in most study subjects (38). The highest dose consisting of 3000 μg altrakincept allowed stabilization of asthma symptoms, despite the absence of any notable change in circulating eosinophil counts or serum IgE levels in these patients.

Conclusion – The effects of altrakincept on asthma were rather minimal, which is why further development of altrakincept was halted (39).

IL-4: AMG-317 (phase 2 completed)
AMG-317 has been tested in asthma in three phase-1 trials and one double-blind phase-2 RCT in patients with moderate-to-severe asthma (40, 41). The phase-2 trial ($n = 294$) failed to demonstrate a significant improvement in asthma following AMG-317 treatment, as assessed by the asthma control questionnaire (ACQ) and FEV1. However, a subgroup analysis showed that patients with baseline ACQ scores in the top tertile significantly improved their ACQ score and patients receiving the highest dose of AMG-317 showed a trend toward improvement in FEV1 and reduction in exacerbations (41). Thus, patients with a higher baseline ACQ tended to respond better to AMG-317 and, in the group administered 300 mg AMG-317, FEV1 and PEF were improved compared to placebo (41). Moreover, a dose-dependent reduction in IgE levels was observed, which, however, did not correlate with FEV1 or ACQ (41).

Conclusion – Although the phase-2 trial using AMG-317 in moderate-to-severe asthma did not find any significant benefits overall, some subgroups appeared to benefit from the treatment, such as patients with high baseline ACQ. Further trials with subgrouping of patients and using perhaps higher doses are necessary.

IL-4: Dupilumab (phase 2 ongoing)
A recent double-blind, parallel-group phase-2a RCT assessed the efficacy of dupilumab in 104 patients with moderate-to-severe asthma and elevated blood or sputum eosinophil counts, in which asthma persisted despite the use of medium to high doses of ICS and LABA (42). The study consisted of a 12-week intervention and an 8-week follow-up period. At week 4, LABA was discontinued and, through weeks 6–9, ICS was gradually reduced. The authors reported that asthma exacerbations, the primary outcome of the study, were 87% lower in the dupilumab group than in placebo, including a significant improvement in FEV1, morning PEF, the ACQ-5, and exhaled nitric oxide (FeNO). Serum levels of CCL17, CCL26, and IgE were also reduced. There was no change in peripheral blood eosinophil counts.

Conclusion – Although this first study showed beneficial effects, experience with more patients and longer intervention time is necessary to conclude on the efficacy of dupilumab in patients with moderate-to-severe asthma.

IL-4: Pascolizumab (phase 2 completed, development halted)
Despite promising preclinical studies, a double-blind phase-2 RCT in patients ($n = 120$) with symptomatic steroid-naïve asthma failed to provide any clinical benefit with pascolizumab (43).

Conclusion – Pascolizumab failed to show any significant clinical improvement in patients with asthma, and its development for asthma was halted.

IL-4: Pitrakinra (phase 2b completed)
Two double-blind, parallel-group phase-2a RCTs assessed safety and efficacy of pitrakinra in patients (total $n = 56$) with asthma, reporting that inhaled pitrakinra increased FEV1 during the late asthmatic response and decreased levels of FeNO (44). Patients receiving pitrakinra experienced fewer asthma-related symptoms and were able to reduce rescue medications, although pitrakinra had no effect on airway hyper-responsiveness or blood IgE levels.

However, a recent placebo-controlled phase-2b RCT ($n = 534$) did not show any effect of inhaled pitrakinra on asthma exacerbations during a 12-week period, which constituted the primary outcome (45). Yet, a subgroup analysis showed a significant reduction in the incidence of asthma exacerbation in patients with blood eosinophilia. A pharmacogenetic analysis in 407 subjects with moderate-to-severe asthma from above study showed that in patients with a specific *IL4Ra* genotype (rs8832GG), pitrakinra was able to reduce asthma exacerbations and decrease symptoms including nocturnal awakenings (45).

Conclusion – Pitrakinra showed promising results in a subgroup of patients with asthma and blood eosinophilia. However, the long-term effects and pharmacodynamics of pitrakinra require further investigations, as systemic application of pitrakinra leads to a quick degradation of this IL-4 mutein, which in turn requires daily administration. Currently, there are no ongoing studies investigating the use of pitrakinra in patients with asthma.

IL-4/IL-13: QBX258 (phase 1 completed, phase 2 ongoing)
QBX258 is a combination of QAX576 and VAK694. No results have yet become available from a phase-1 study that is completed and a phase-2 study that is recruiting currently, assessing safety and efficacy of QBX258 in patients with asthma (46, 47).

IL-5: Benralizumab (MEDI-563; phase 1 completed, phase 2/3 ongoing)
As of to date, three studies have been completed, assessing the safety of benralizumab. An open-label phase-1 study ($n = 44$) used increasing IV doses and observed an efficacy in patients with mild asthma along with a reduction in peripheral blood eosinophil counts and eosinophil cationic protein (48).

In a multicenter phase-1 RCT ($n = 13$), asthma patients were randomized to three monthly subcutaneous (SC) injections of placebo *vs* 100 or 200 mg benralizumab. Single-dose IV and multiple-dose SC benralizumab reduced eosinophil counts in airway mucosa and submucosa and in sputum and suppressed eosinophil counts in bone marrow and peripheral blood (49).

Currently, a multicenter phase-2 RCT is ongoing, assessing safety and efficacy of IV benralizumab following an acute asthma exacerbation (50).

Conclusion – Available clinical data are sparse, and further RCTs are needed to assess the role of benralizumab in asthmatic patients. Three phase-3 efficacy and safety studies of benralizumab are currently ongoing (51–53).

IL-5: Mepolizumab (phase 2 completed, phase 3 ongoing)
Four RCTs using mepolizumab in asthma patients have been conducted so far. A first multicenter RCT in patients ($n = 362$) with moderate persistent asthma treated with mepolizumab 250 or 750 mg once monthly IV for 3 months failed to demonstrate any notable improvement in asthma symptoms, but showed significant effects on eosinophil counts in sputum and blood (54).

However, three recent RCTs reported a significant benefit of mepolizumab in eosinophilic asthma (43, 55–57). In a double-blind, parallel-group RCT ($n = 20$), mepolizumab was used in a subgroup of chronic severe asthma patients with airway eosinophilia and frequent exacerbation despite ICS and systemic corticosteroids (55). Monthly IV injections of mepolizumab 750 mg for 4 months caused a significant decrease in blood and sputum eosinophils. These changes were accompanied by a significant reduction in asthma exacerbations and corticosteroid use and a significant improvement in FEV1 and the asthma control score.

Similarly, another double-blind, parallel-group RCT ($n = 61$) reported a significant decrease in asthma exacerbations as well as a marked reduction in blood and sputum eosinophilia in asthma patients receiving 750 mg mepolizumab monthly for 1 year (56).

A recent multicenter RCT (DREAM study) assessing mepolizumab in 621 patients with severe, exacerbation-prone eosinophilic asthma showed an effective decrease in the frequency of asthma exacerbations along with a significant decrease in blood and sputum eosinophilia (57).

Conclusion – The current data demonstrate that mepolizumab is effective in patients with eosinophilic asthma characterized by frequent exacerbations and persistent, steroid-resistant eosinophilia.

IL-5: Reslizumab (phase 3 completed)
A recent multicenter phase-2 RCT evaluated IV reslizumab in patients with eosinophilic asthma with persistent symptoms despite high-dose ICS. Compared to placebo ($n = 53$), reslizumab ($n = 53$; 3 mg/kg) exhibited a significant decrease in sputum eosinophilia together with a nonsignificant improvement in asthma control as assessed by the ACQ, the primary study endpoint, and a nonsignificant reduction in asthma exacerbations (58). In patients with concomitant NP and high blood and sputum eosinophil counts, reslizumab treatment significantly improved asthma symptoms. These data led to the initiation of several phase-3 RCTs using reslizumab that are currently completed or ongoing (59).

Conclusion – Reslizumab appears to be effective in asthma patients with sputum eosinophil levels of 3% and more, which needs further confirmation in larger RCTs.

IL-9: Enokizumab (MEDI-528; phase 2b completed)
Four clinical trials have evaluated the effects of enokizumab on asthma, namely two phase-1 and two phase-2 studies.

The phase-2 trials (total $n = 47$) found no significant improvement in the asthma symptom score following enokizumab, although there were some indications that enokizumab was able to reduce exacerbations and improve the asthma symptom score (60, 61). A limitation of these trials consisted in the low number of patients enrolled. Of note, one of the trials was stopped before reaching the end, which was due to a patient showing a conspicuous pontine lesion on MRI that turned out to be an artifact (60).

A recent multicenter phase-2b RCT including 329 subjects with uncontrolled asthma demonstrated that enokizumab

failed to show any improvement in asthma symptoms, FEV1, or reduced asthma exacerbations compared to placebo (62).

Conclusion – Currently, completed trials provided negative results. Further studies are needed to evaluate whether enokizumab might benefit a certain endotype of asthma.

IL-13: ABT-308 (phase 1 completed)

Currently, a phase-1 RCT investigating safety, tolerability, and pharmacokinetics of ABT-308 in asthma is completed, but results have not become available yet (63).

IL-13: Anrukinzumab (IMA-638, phase 2 completed), IMA-026 (phase 1 completed)

A parallel-group phase-1/2 RCT in patients with mild asthma compared IMA-638 (anrukinzumab, $n = 27$) and IMA-026 ($n = 29$) with placebo (64). The biologicals were administered on days 1 and 8, and allergen challenge was performed on days 14 and 35. Primary endpoint was the late asthmatic response. Secondary endpoints included early asthmatic response, bronchial hyper-responsiveness (BHR), sputum eosinophils, safety, and tolerability. IMA-638 significantly attenuated the early and late asthmatic responses on day 14, whereas IMA-026 did not affect the early and, only minimally, the late asthmatic responses. Both drugs failed to show an effect on BHR, blood and sputum eosinophils, and total IgE.

Conclusion – Some of the results of anrukinzumab are promising, but further studies are needed to determine its use in asthma.

IL-13: CNTO-5825 (phase 1 completed)

CNTO-5825 was tested in a phase-1 RCT ($n = 64$) in healthy and nonsymptomatic atopic patients, assessing its safety, tolerability, immunogenicity, and efficacy (65). Compared to placebo, CNTO-5825 led to a significant decrease in serum IgE levels.

IL-13: GSK679586 (phase 2, completed)

Following a phase-1 RCT, assessing safety and tolerability in healthy ($n = 32$) and mild asthmatic subjects ($n = 28$) (66), a phase-2 RCT ($n = 198$) investigated the efficacy and safety of GSK679586 in patients with severe asthma receiving high-dose ICS of 1000 μg/d and more (67). Primary endpoint was the change in ACQ-7 over 12 weeks. The study found no statistically significant improvement in ACQ-7, FEV1, asthma exacerbation rate, serum IgE levels, or blood eosinophil counts. The authors suggested that this might be due to the high-dose ICS treatment, which already reduced IL-13.

Conclusion – A recent phase-2 study reported a lack of efficacy of GSK679586 in patients with severe asthma. Further studies should evaluate whether GSK679586 might benefit certain subgroups of asthma patients.

IL-13: Lebrikizumab (phase 2 completed, phase 3 ongoing)

Lebrikizumab has been tested in a multicenter RCT in 219 adults with asthma (9). Patients with uncontrolled moderate-to-severe asthma receiving lebrikizumab (in addition to standard inhalation therapy) showed a significant increase in FEV1. The increase in FEV1, along with a significant reduction in FeNO, IgE levels, CCL13, and CCL17, was most notable for patients showing high pretreatment serum levels of periostin (9). Notably, periostin correlates with IL-13 levels (68), suggesting it might serve as a biomarker in clinical practice to determine the asthma endotype, which is most sensitive to lebrikizumab treatment. However, exacerbation rates or asthma symptoms were not found to be significantly reduced in this study (9).

In a recent dose-ranging study in asthmatic patients ($n = 212$), lebrikizumab led to an increase in FEV1 in patients with high periostin serum levels although the difference was not statistically or clinically significant in comparison with patients with low periostin serum levels (69).

Conclusion – Although first results are promising in patients showing high periostin serum levels, further studies are needed to evaluate the efficacy of lebrikizumab in asthma.

IL-13: QAX576 (phase 2 ongoing)

No results have yet been published from two phase-2 studies that are investigating safety, tolerability, and efficacy of QAX576 in asthma (70, 71).

IL-13: Tralokinumab (CAT-354; phase 2a completed, phase 2b ongoing)

In a parallel-group multicenter RCT, 194 subjects with moderate-to-severe asthma were randomized to either tralokinumab (150, 300 or 600 mg) or placebo (68). Primary endpoint was the change from baseline in the mean ACQ-6. No improvement in ACQ-6 was found in the tralokinumab group. However, subjects treated with tralokinumab showed an improvement in FEV1 and reduced use of rescue medication.

Conclusion – Further studies are needed to evaluate whether tralokinumab might benefit a subset of asthma patients, such as those with increased periostin levels.

IL-17: Brodalumab (AMG-827; phase 2 completed)

In a recent phase-2 RCT, 302 subjects with inadequately controlled asthma were randomized to brodalumab (140, 210 or 280 mg) or placebo. Primary outcome was ACQ, and secondary outcomes included FEV1, symptom scores and symptom-free days. The study failed to demonstrate any difference between the groups; however, subgroup analysis showed a trend for ACQ improvement only in the high-reversibility subgroup (postbronchodilator FEV1 improvement ≥20%) (72).

Safety and kinetics of brodalumab have been evaluated positively in patients ($n = 198$) with psoriasis (73).

Conclusion – Further studies are needed to assess the efficacy of brodalumab in asthma, especially in the group of asthma patients with high reversibility. Indeed, a phase-2 trial of brodalumab in subjects with inadequately controlled asthma showing high reversibility is recruiting participants (39).

IL-17: Secukinumab (AIN457; phase 2 ongoing)

No completed studies using secukinumab in asthma have so far been reported. There is an ongoing multidose phase-2

RCT, recruiting participants with inadequately controlled asthma receiving ICS and LABA (74). Its primary endpoint is the change in ACQ, and its secondary endpoints include FEV1, FeNO, and sputum neutrophils, as well as tolerability and safety.

Safety and efficacy of secukinumab were previously assessed in patients with ankylosing spondylitis ($n = 30$) (75).

Conclusion – No data are currently available, assessing the role of secukinumab in asthma.

OX40L: huMAb OX40L (phase 2 completed)

A phase-2 RCT in patients ($n = 28$) with mild asthma investigated efficacy, safety, and tolerability of huMAb OX40L, given IV over 3 months, with allergen challenges performed on days 56 and 113 (76). Primary endpoint was the late-phase asthmatic response; secondary endpoints included early-phase asthmatic response, BHR, serum IgE, and blood and sputum eosinophils. huMAb OX40L did not reach the primary or most of secondary endpoints. Only serum IgE levels were significantly reduced after the second allergen challenge, while effects on eosinophils were inconclusive. Although huMAb OX40L significantly reduced sputum eosinophils before the allergen challenge, no difference was found following the challenge.

Conclusion – Although the results of a first phase-2 trial do not support its use in mild asthma, further studies are needed to assess the efficacy of (higher doses of) huMAb OX40L in moderate-to-severe asthma.

TNF: Etanercept (phase 2 completed)

The use of etanercept in patients with moderate-to-severe or refractory asthma has been evaluated in several trials.

In a first open-label, uncontrolled pilot study ($n = 17$), patients receiving etanercept experienced improvements in subjective asthma control (Juniper ACQ), lung function (PEF, FEV1 and forced vital capacity), and BHR (77).

In a second double-blind, placebo-controlled crossover pilot study ($n = 30$), treatment with etanercept resulted in improvements in asthma control (Juniper ACQ), BHR, and postbronchodilator FEV1 (78).

In a third study ($n = 39$), a slight improvement in ACQ but no differences in asthma QoL, PEF, BHR, or exacerbation rates between etanercept and placebo was reported (79).

The largest study so far evaluating etanercept in asthma ($n = 132$) found no significant difference in prebronchodilator FEV1, ACQ-5, asthma exacerbations, BHR, and asthma QoL (80).

Conclusion – Available data question the use of etanercept in severe asthma. Larger studies are necessary to investigate whether etanercept might benefit a certain asthma endotype.

TNF: Golimumab (phase 2 completed)

Golimumab was evaluated in asthma in a multicenter phase-2 RCT, enrolling 309 patients with severe, persistent asthma (81). Changes in FEV1 and asthma exacerbations were endpoints. No significant differences were observed in any of the endpoints between golimumab and placebo. An increased rate of SAEs was observed in the golimumab treatment group (see section on 'Adverse events'), which led to the interruption of the trial (81).

Conclusion – Golimumab caused an increased rate of SAEs in patients with asthma, which makes future studies evaluating golimumab in asthma rather unlikely.

TNF: Infliximab (phase 2 completed)

A RCT assessed infliximab in 38 patients with moderate asthma that were symptomatic despite receiving ICS (82). PEF, FEV1, FeNO, and asthma exacerbations were evaluated. The group receiving infliximab reported reduced PEF variations and lower asthma-related exacerbations.

Conclusion – Available data are limited to evaluate the therapeutic role of infliximab in asthma. Moreover, administration of another TNF inhibitor (golimumab) in asthma led to an increase in SAEs, thus cautioning the use of TNF inhibitors in asthma.

TSLP: AMG-157 (phase 1 completed)

A phase-1 RCT assessed the use of AMG-157 in 31 patients with mild asthma who were assigned to receive placebo or AMG-157 IV three times a month (83). All patients underwent an allergen challenge on days 42 and 84. Primary endpoint was the late asthmatic response; secondary endpoints included early asthmatic response, safety, AEs, and immunogenicity; and exploratory endpoints comprised BHR, FeNO, total serum IgE, sputum and blood eosinophils, Th2 cell counts, and ratio of Th2 to Th1 cells in blood. This study showed in the late and early asthmatic responses that, in comparison with placebo, AMG-157 reduced the maximum decreases in FEV1 following an allergen challenge by 34% on day 42 and 46% on day 84, although no significant changes were noted in FEV1 before the allergen challenges. The reason why AMG-157 was unable to change the baseline FEV1 may be due to the fact that the recruited patients had near-normal FEV1 values at the beginning of the study. Furthermore, AMG-157 led to a significant decrease in blood and sputum eosinophil counts and FeNO, while no significant changes were noted in total IgE levels and the Th2-to-Th1 ratio.

Conclusion – Although the results seem promising, further studies are needed to evaluate the use of AMG-157 in patients with severe asthma. A phase-2 RCT is currently recruiting.

Allergic rhinitis

IgE: Omalizumab (phase 2 completed)

A RCT ($n = 536$) assessed the efficacy of omalizumab on symptoms of SAR in 25 centers in the USA (84). This study showed that during the pollen season, patients with low free IgE following omalizumab experienced significantly fewer symptoms and needed significantly less rescue antihistamine medication compared to placebo.

Another RCT ($n = 251$) investigated the use of omalizumab in SAR in birch pollen-sensitized patients in Scandinavia (85). In this study, clinical efficacy was related to

free IgE levels. Thus, the average daily nasal symptom severity score, average daily number of tablets of rescue antihistamines, and proportion of days with medication use were significantly lower when serum-free IgE was 25 ng/ml or less.

Similar effects with omalizumab were observed in Japanese patients ($n = 100$) with SAR to Japanese cedar pollen (86). In accordance with the above-mentioned RCT, this study demonstrated that the daily symptoms assessed by daily nasal and daily ocular symptom medication scores, daily nasal symptom severity score, and daily ocular symptom severity score during the pollen season as well as the use of daily nasal and daily ocular rescue medication scores were significantly lower in patients receiving omalizumab (86). Moreover, this study showed a direct correlation of low free IgE and a decrease in symptoms. No antidrug antibodies (ADA) against omalizumab were observed during the course of this study.

Subsequently, the same group of investigators assessed efficacy and immunogenicity of omalizumab when re-administered to 34 patients with SAR to Japanese cedar pollen (87). Retreatment did not induce ADAs and was well tolerated.

Conclusion – In patients with SAR, RCTs have shown omalizumab to reduce nasal symptoms and use of antihistamines, leading to improved QoL (21, 84).

IgE: Omalizumab and specific immunotherapy

The combination of biologicals with SIT is considered to decrease the rate of AEs, prolong efficacy, increase tolerance development, and allow application of SIT to high-risk groups. Currently, clinical trials assessing the combined use of biologicals with SIT are limited to omalizumab treatment during the pre-SIT, dosing-up, and allergen seasonal phases.

A RCT ($n = 159$) investigated the impact of omalizumab on RIT in patients with ragweed-induced SAR (31). Omalizumab was given for 9 weeks prior to RIT and continued for another 12 weeks. Patients receiving RIT plus omalizumab had 40% decrease in overall AEs and 78% decrease in anaphylaxis requiring adrenaline (epinephrine) treatment as compared to RIT alone (31). While allergen-specific IgG4 levels remained unaltered, CD23-dependent IgE–allergen binding on B cells was completely blocked under omalizumab and RIT (88).

A second study ($n = 140$) compared grass and rye allergen SIT with or without omalizumab, demonstrating that addition of omalizumab showed an intraseasonal positive effect on the severity of symptoms (89). However, this effect was not lasting, as no difference was observed between the groups in the following extension seasons, during which both groups only received SIT without omalizumab (90). Interestingly, SAR patients belonging to the former SIT plus omalizumab group were found to have a slight increase in FEV1 in the follow-up period.

A third study ($n = 221$), conducted in children aged 6–17 years, contained four treatment arms, including birch allergen SIT, grass allergen SIT, birch allergen SIT plus omalizumab, and grass allergen SIT plus omalizumab (91). Both SIT groups receiving omalizumab showed a significant reduction in symptoms during the pollen seasons compared to SIT only. The need of antihistamine rescue medication in the omalizumab-treated SIT groups was particularly low. Furthermore, seven patients developed eczema on SIT only, while the groups receiving concomitant omalizumab remained free of eczema.

Conclusion – The combination of omalizumab with SIT showed a positive effect on SAR symptoms and SIT-related AEs. However, the beneficial effects of omalizumab appear to be temporary.

IgE: Quilizumab (phase 1b completed)

A phase-1b RCT ($n = 36$) assessed safety, tolerability, and pharmacokinetics of quilizumab in patients with allergic rhinitis (6). Primary endpoints were safety and tolerability of IV and SC quilizumab. The trial showed a significant reduction in total and allergen-specific IgE levels and an acceptable safety profile.

IL-4: VAK694 (phase 2 completed)

A phase-2 RCT investigated 37 grass pollen-monosensitized SAR patients receiving placebo, SIT, or SIT plus VAK694; however, the results of this study have not been published yet (92).

IL-13: QAX576 (phase 2 completed)

The results of a phase-2 proof-of-concept study investigating the efficacy of QAX576 in patients with SAR have not been published yet (93).

Food allergy

IgE: Omalizumab (phase 2 completed/stopped)

A parallel-group phase-2 RCT assessing the use of omalizumab in peanut allergic patients ($n = 45$) had to be stopped because two severe allergic reactions occurred during a first oral peanut allergen challenge (94). Nevertheless, analysis of 14 patients that finalized the study, including a second oral food challenge, showed that omalizumab led to a larger increase in the tolerability of peanut allergen upon oral food challenge compared to placebo.

Conclusion – Omalizumab increases the tolerability in patients with food allergy, as assessed in 14 patients. Further studies are needed involving a larger patient collective.

IgE: Omalizumab and specific immunotherapy (phase 2)

Neither oral immunotherapy (OIT) nor sublingual immunotherapy is currently recommended for routine clinical use in food allergic patients due to a high risk of AEs. Moreover, SIT-induced tolerance quickly disappears after cessation of SIT (95). Nevertheless, recent studies showed that the combination of OIT with anti-IgE strategies might be a promising therapeutic approach (96–98).

Omalizumab treatment combined with milk OIT in children ($n = 11$) allergic to cow's milk led to rapid desensitization in most patients within 7–11 weeks (96). Nine of 10

patients who completed the study passed a double-blind placebo-controlled food challenge and an open challenge with milk without showing any symptoms; these patients subsequently introduced and tolerated normal amounts of milk in their diet. Tolerance induction correlated with a reduction in milk-specific IgE, an increase in milk-specific IgG4, and a decrease in milk-specific T-cell responses, the latter of which shifted from IL-4 to interferon-γ production (99).

This proof-of-concept study was followed by other clinical trials in patients with milk or peanut allergy, assessing whether a combination of IgE targeting and OIT represents a useful therapeutic option for patients with severe food allergies (100).

Conclusion – Results from studies with omalizumab-combined OIT are promising, which await confirmation by further studies.

Hymenoptera allergy

IgE: Omalizumab and specific immunotherapy (case reports)
Currently, six case reports have been published, investigating the effects of combining venom-specific immunotherapy (VIT) with omalizumab with somewhat mixed results (101–103). These case studies were conducted in patients (between 15 and 45 years of age) suffering from bee venom allergy who either developed severe AEs to or failed to respond to rush or ultra-rush VIT. Omalizumab was administered at a dose of 150 mg every 2 weeks, starting 6 weeks prior to VIT and continuing for the duration of VIT (103). While this combination seemed to be protective in a patient when stung by a bee after 12 months on treatment, reduction in omalizumab to 75 mg after 24 months led to an anaphylactic reaction upon VIT in that same patient (103). Alternatively, another report used a single dose of 300 mg omalizumab 2 weeks prior to VIT, which allowed the patient to tolerate the maximum dose of ultra-rush VIT (101). Similarly, in a third report, a patient with mastocytosis and bee venom allergy was administered monthly 300 mg omalizumab prior to VIT (initially 7 days and then at shorter intervals up to 40 min prior to VIT), which resulted in the patient tolerating VIT and led to a decrease in patient's serum tryptase levels (102). Subsequent reduction in the dose of omalizumab to 150 mg in the same patient led upon VIT to extended flushing, transient mild tachycardia, injection site reaction, and a mild increase in tryptase, which is why the authors returned to the 300 mg dose for subsequent administrations, under which therapy VIT-related AEs did not occur (104).

Contrarily, another case report failed to demonstrate a positive effect of combining 300 mg omalizumab, once monthly, with ultra-rush VIT, as even following the addition of omalizumab, the patient was unable to tolerate the maintenance dose of VIT (105).

Conclusion – On the basis of the present case reports, it is not possible to draw a firm conclusion on whether VIT should be combined with omalizumab. Randomized controlled trials are needed to evaluate the effect of this combination treatment in patients with hymenoptera allergy.

Urticaria and urticarial syndromes

Chronic urticaria comprises chronic spontaneous urticaria (CSU, also termed chronic idiopathic urticaria), chronic inducible urticaria (CindU), and chronic autoimmune urticaria (CAU). Chronic autoimmune urticaria makes up for about 40–45% of patients with chronic urticaria and usually presents with autoantibodies against the high-affinity IgE receptor FcεRI, suggesting an underlying autoimmune etiology.

CD20: Rituximab (phase 1/2 suspended)
Rituximab has shown some efficacy in a limited number of patients with CAU, but not in CSU (106–108).

Conclusion – Controlled clinical trials are needed to evaluate the efficacy of rituximab in chronic urticaria, including CSU and CAU.

IgE: Omalizumab (phase 3 completed, phase 4 ongoing)
Several studies have demonstrated the safety and efficacy of omalizumab in patients with moderate-to-severe CSU refractory to standard treatment.

In a multicenter phase-3 RCT, omalizumab at doses of 150 or 300 mg significantly improved CSU in a dose-dependent manner in patients ($n = 323$) who had previously been symptomatic despite the use of licensed doses of H1-antihistamines (109).

Another multicenter phase-3 RCT ($n = 336$) investigated safety, tolerability, and efficacy of 300 mg omalizumab in patients with CSU who remained symptomatic despite treatment with up to four times the licensed doses of H1-antihistamines, in addition to an H2-antihistamine, leukotriene receptor antagonist, or both (110). Patients receiving omalizumab experienced a significant reduction in symptoms, including days free of urticaria and angioedema. After discontinuation of omalizumab, symptoms gradually recurred over a period of about 10 weeks to levels similar to those observed with placebo.

Recently, a real-life retrospective analysis ($n = 51$) indicated that omalizumab was a safe and rapidly and highly effective treatment in both CSU and CindU (111). Interestingly, efficacy did not correlate with baseline IgE levels. Other smaller studies (total $n = 25$) reported on several beneficial effects of omalizumab, such as reduced need of immunosuppression and H1-antihistamines and sustained long-term efficacy for patients with severe therapy-resistant CSU (112, 113).

Several case reports have shown efficacy in the treatment of different types of CindU using omalizumab (114–116). Moreover, a trial enrolling seven patients with recalcitrant CindU showed a significant improvement in symptom control upon omalizumab treatment (117).

Omalizumab has shown some efficacy in a small exploratory proof-of-concept study in 12 patients with CAU resistant to H1-antihistamines (118). More recently, omalizumab was found to be effective in improving urticarial symptoms in a subset of patients ($n = 49$) with CAU expressing IgE-type autoantibodies to thyroid peroxidase (117).

Conclusion – Based on the available data, omalizumab seems to be safe and effective in the treatment of refractory CSU and CAU, and might be useful in CindU. Accordingly, the revised international treatment guidelines for the management of urticaria recommend omalizumab as third-line therapy (119).

IgE: Quilizumab (phase 2 ongoing)
A phase-2 RCT investigating the safety and efficacy in patients with CSU refractory to H1-antihistamine treatment is currently ongoing, but no results have become available yet (120).

IL-1: Anakinra, canakinumab (phase 2 completed), and rilonacept (phase 2 completed)
Several diseases and well-characterized autoinflammatory syndromes can be associated with urticaria and angioedema, although these pathologies are no longer considered subtypes of urticaria. A detailed discussion of biologicals used for the treatment of autoinflammatory diseases is beyond the scope of this article and has been recently reviewed (121, 122). Overall, targeting IL-1 signaling has significantly improved the outcome of patients with autoinflammatory syndromes.

For Schnitzler's syndrome, a recent expert consensus panel agreed that anakinra should be used as the first-line treatment in patients with significant impairment of QoL or regularly elevated inflammation markers (123). Moreover, an open-label study using rilonacept in eight patients with Schnitzler's syndrome demonstrated a rapid and significant clinical improvement (124). In another open-label, single-treatment arm trial including eight patients with Schnitzler's syndrome, monthly injections of 150 mg canakinumab proved to be effective and well tolerated (125).

In urticarial vasculitis, treatment of 10 patients using canakinumab within an open-label trial was shown to be safe and efficacious for this disease (126).

Conclusion – IL-1-targeting biologicals have provided very promising results in treating autoinflammatory disorders, including those associated with urticaria.

TNF: Adalimumab, etanercept, and infliximab (all: case reports)
In an observational study of 20 adult patients with chronic urticaria, 16 patients with CSU, two patients with CAU, one patient with delayed pressure urticaria, and one patient with neutrophilic urticaria, TNF inhibitors were shown to result in complete or almost complete resolution of urticaria in 60% of patients, while partial response was found in another 15% of patients (127). In another small series, six patients affected by CSU or urticarial vasculitis unresponsive to other immunosuppressive therapies experienced a significant clinical improvement when given TNF inhibitors (128). Furthermore, two case reports have shown efficacy of TNF inhibitors in delayed pressure urticaria and cold contact urticaria (129, 130).

Conclusion – Controlled studies are needed to assess the efficacy of TNF inhibitors in patients with chronic urticaria.

Atopic dermatitis

CD2: Alefacept (case reports, development halted)
In an open-label pilot study, 10 patients with moderate-to-severe AD not adequately responding to topical corticosteroid therapy and/or calcineurin inhibitor therapy were treated with 12 weekly intramuscular injections of 15 mg alefacept. This resulted in an improvement in the clinical severity of AD, and a reduction in skin T cells and T-cell activation markers (131).

In another open-label study, nine patients with moderate-to-severe AD were treated with 30 mg alefacept intramuscularly; only two of nine patients demonstrated a significant clinical response (132).

In 2011, alefacept was removed from the market due to insufficient market.

Conclusion – Inhibition of T-cell activation and migration to the skin by blocking CD2−LFA-3 interaction provide a possible target for treating AD although, following the withdrawal of alefacept from the market, there is currently no biological targeting these molecules.

CD11a: Efalizumab (case reports, withdrawn)
In a systematic retrospective study of medical files of AD patients, only two of eleven patients demonstrated an improvement in AD following treatment with efalizumab (133).

In a prospective, open-label pilot study enrolling 10 subjects with severe AD, significant clinical improvement was demonstrated in six of 10 patients (134).

Conclusion – Although efalizumab showed some effects in AD, this biological has been withdrawn from the market as it was associated with progressive multifocal leukoencephalopathy (135).

CD20: Rituximab (case reports)
The first study using rituximab in patients with severe AD was an open-label pilot study including six patients administered twice 1 g rituximab IV 2 weeks apart (136). All patients experienced an improvement in skin lesions, pruritus, and skin texture, and were able to reduce their use of corticosteroids, with effects lasting for at least 24 weeks. Although allergen-specific IgE levels remained unchanged, the authors suggested that the results were due to a reduction in both B- and T-cell responses in blood and skin.

Conversely, another case report including two patients with severe AD found no response to rituximab 500 mg. The lack of efficacy of rituximab in this report, in comparison with the above-mentioned one, might be due to a lower dose of rituximab used and a likely higher disease severity of the patients from the second study (137).

A recent single-center observational study used a combination of omalizumab and rituximab in six patients with severe AD, leading to an improvement in pruritus, skin lesions, and QoL (138). The rationale for this combination consisted in rituximab reducing B cells and T-cell responses, while omalizumab targets IgE levels.

Conclusion – Despite the presence of some promising data, larger RCTs are needed to investigate the effect of rituximab on AD.

IgE: Omalizumab (phase 4, completed)
The results on the use of omalizumab in patients with AD are controversial (21). A 28-week open-label trial using omalizumab in 20 adults with moderate-to-severe AD found that a positive response was most notable in a subgroup of patients not carrying a filaggrin mutation (139). Conversely, a double-blind RCT enrolling 20 AD patients did not find any positive effect following omalizumab (140), which the authors concluded might be due to the difference between acute and chronic AD, as this study only included chronic AD patients, unlike previous trials involving patients with acute AD. Interestingly, most AD patients resistant to omalizumab treatment had very high pretreatment IgE levels, which might explain treatment failure (21). In another open-label trial, 11 AD patients with high IgE levels received low-dose omalizumab for 20 weeks, with six patients responding positively to the treatment, while the others experienced worsening or no improvement, leading the authors to suggest that omalizumab was only slightly better than placebo (141).

Conclusion – Further studies are needed to clarify the effects of omalizumab in acute and chronic AD.

IgE: QGE031
A phase-2 RCT evaluating the efficacy and safety of QGE031 in patients with moderate-to-severe AD has been completed (142), but the results have not been published yet.

IL-4: Dupilumab (phase 2 completed)
A recent publication summarizing four phase-1/2 RCTs (total $n = 207$) showed that dupilumab at 300 mg led to a marked and rapid improvement in pruritus scores, the eczema area and severity score by 50%, and investigator's global assessment in moderate-to-severe AD, either as a monotherapy for four or 12 weeks or in combination with topical corticosteroids for 4 weeks (143). Moreover, patients receiving dupilumab had less frequent skin infection compared to placebo.

Conclusion – These studies indicate that dupilumab may be a good consideration in patients with moderate-to-severe AD, leading to marked improvement in skin lesions and pruritus as well as a reduction in skin infections. Further studies enrolling more patients are needed to confirm these promising results.

IL-5: Mepolizumab (phase 2 completed)
In a RCT in AD patients ($n = 43$), two single doses of 750 mg mepolizumab, given 1 week apart, caused a significant decrease in blood eosinophils and, to a lesser extent, tissue eosinophils (144, 145). However, clinical improvement was not achieved, possibly due to the relatively short duration of mepolizumab treatment.

IL-12/IL-23: Ustekinumab (phase 2 ongoing)
On the basis of two off-label case studies demonstrating a clinical benefit of ustekinumab in two patients with AD (146, 147), two phase-2 RCTs using ustekinumab in AD are currently ongoing (148).

IL-22: ILV-094 (phase 2 recruiting)
A phase-2 RCT to determine safety, tolerability, pharmacodynamics, and clinical efficacy of ILV-094 in AD is currently recruiting (149).

IL-31: BMS-981164 (phase 1 ongoing) and CIM331 (phase 2 ongoing)
A phase-1 RCT assessing the safety of BMS-981164 is currently ongoing (150). Moreover, CIM331 is currently being tried in a phase-2 RCT for efficacy in treating AD (151). Results of these studies have not become available yet.

TNF inhibitors (case reports)
The TNF inhibitors infliximab ($n = 9$) and etanercept ($n = 2$) have been evaluated in pilot studies in both children and adults with AD, showing a poor therapeutic benefit of these biologicals for AD (152, 153). Only two of nine treated adults demonstrated some improvement. Importantly, in both treated children flare-ups of both bacterial and viral infections were observed during TNF inhibitor treatment.

Conclusion – Based on pilot studies, TNF inhibitors do not appear to be beneficial in treatment of AD. The reason for this failure of TNF-targeting agents in AD might be due to either a limited role of TNF in AD inflammation or the increased frequency of bacterial and viral infections following TNF blockade, thus driving AD.

TSLP: AMG-157 (phase 1 completed)
A phase-1 study evaluated the safety of AMG-157 in healthy and AD patients (154); however, results have not become available yet.

Eosinophilic disorders

Allergic bronchopulmonary aspergillosis

IgE: Omalizumab (phase 4 completed). Most of the trials assessing omalizumab in allergic bronchopulmonary aspergillosis (ABPA) were performed in patients with ABPA and cystic fibrosis. Some case reports and case series demonstrated a benefit of omalizumab in children with cystic fibrosis and ABPA as treatment with omalizumab resulted in improved FEV1, fewer respiratory symptoms, and decreased use of corticosteroids (155–158). Conversely, one report showed no improvement in ABPA in a patient with cystic fibrosis receiving omalizumab (159), which may be due to omalizumab being efficacious in the acute, but not chronic phase of ABPA (21).

However, a Cochrane review including only one eligible trial enrolling 14 patients reported that there was a lack of evidence pertaining to the efficacy and safety of omalizumab therapy in patients with cystic fibrosis and ABPA (160).

Likewise, there are only a few studies on the efficacy of omalizumab in the treatment of ABPA in asthmatic patients not affected by cystic fibrosis (161–164). Although the number of patients included was rather small, these trials showed an improvement in daily asthma symptoms and FEV1, and a

reduction in oral corticosteroid use and asthma exacerbations. This was accompanied by a reduction in inflammatory markers, blood eosinophilia, total serum IgE levels, and FeNO.

Both in patients with asthma and ABPA, the optimal dose of omalizumab remains controversial. In asthma patients with serum IgE levels between 30 and 700 IU/ml, the proposed dose is based on pretreatment IgE levels and body weight and varies between 225 and 600 mg. However, patients with ABPA often show serum IgE levels of 1000 IU/ml and more, suggesting that higher omalizumab doses are needed (165). A recent case report obtained a good clinical response in a patient with ABPA and cystic fibrosis by calculating the monthly dose of omalizumab using 0.016 mg per kg body weight per IgE IU/ml (156).

Conclusion – Omalizumab seems to be a potential alternative to corticosteroids for patients with ABPA. Future studies including RCTs are needed to determine the efficacy of omalizumab in ABPA.

Eosinophilic granulomatosis with polyangiitis

Patients affected by eosinophilic granulomatosis with polyangiitis (EGPA; formerly called Churg–Strauss syndrome) often present with an atopic background and almost all have asthma, in addition to showing marked blood eosinophilia.

IgE: Omalizumab (case studies). A few case reports provided evidence supporting the use of omalizumab in EGPA as an adjuvant therapy in adults and children (166–170). These papers suggested that omalizumab probably acted by blocking IgE-mediated eosinophil accumulation and proliferation in EGPA.

IL-5: Mepolizumab (phase 2 completed, phase 3 ongoing). In a case report of a 28-year-old female patient with EGPA, monthly infusions of 750 mg mepolizumab reduced peripheral blood eosinophil counts to normal levels after a month and resolved the patient's asthma symptoms after 6 months, which was paralleled by a radiographic improvement in lung parenchyma (171).

In an open-label pilot study, seven patients were treated with four monthly infusions of 750 mg mepolizumab. The treatment resulted in 64% and 61% decreases in corticosteroid use at 12 and 24 weeks, respectively, along with a reduction in eosinophilia; however, these effects reversed and exacerbations recurred upon cessation of the drug (172, 173).

Conclusion – Although some evidence suggests a benefit of using mepolizumab in EGPA, available data are too limited to reach a conclusion.

Nasal polyposis

IgE: Omalizumab (phase 2 completed). A retrospective pilot study in atopic patients with comorbid asthma examined whether omalizumab was efficacious in the management of NP previously treated with endoscopic surgery. Four patients were given omalizumab postoperatively and compared to four control subjects. Nasal symptom scores improved in the omalizumab group, but no significant improvement was seen in sinus computed tomography (CT) in either group (174).

Recently, a phase-2 RCT evaluated the efficacy of omalizumab in patients with NP ($n = 24$) also suffering from asthma (25). This study reported positive results in the omalizumab-treated group, including a significant decrease in total nasal endoscopic polyp scores further confirmed by CT after 16 weeks on omalizumab. Omalizumab had also a beneficial effect on nasal and asthma symptoms and QoL scores, irrespective of the presence of atopy.

Conclusion – Omalizumab may be considered in carefully selected patients with inadequately controlled chronic rhinosinusitis with NP and comorbid asthma in atopic and nonatopic patients.

IL-5: Mepolizumab (phase 1/2 completed). Mepolizumab was assessed in a recent RCT in 30 patients with severe NP refractory to corticosteroid treatment. Two single IV injections of 750 mg mepolizumab resulted in significant improvement in NP and CT scan scores in 12 of 20 patients receiving mepolizumab compared to only one of 10 patients receiving placebo (175).

Conclusion – Promising results were obtained with the use of mepolizumab in patients with severe chronic rhinosinusitis and NP. Larger RCTs are needed to determine the efficacy of mepolizumab in NP.

IL-5: Reslizumab (phase 1/2 completed). The safety, pharmacokinetics, and biologic activity of a single IV dose of reslizumab (1 or 3 mg/kg) were investigated in 24 subjects with bilateral NP in a two-center RCT (176). Reslizumab treatment reduced peripheral blood eosinophil counts along with eosinophil cationic protein concentrations in nasal secretions. A significant reduction in the size of individual nasal polyps occurred in half of the treated patients, with responders exhibiting increased IL-5 concentrations in nasal secretions prior to treatment. Thus, IL-5 levels in nasal secretion might be considered a possible biomarker in future clinical trials using IL-5 antagonists.

Conclusion – Further studies are necessary to evaluate whether reslizumab might be beneficial in patients with NP.

Hypereosinophilic syndromes

CD52: Alemtuzumab (case reports). The use of alemtuzumab in hypereosinophilic syndromes (HES) is considered off-label. Two case reports and one observational study with 11 patients found promising results in patients with HES with complete normalization of blood eosinophil counts in over 90% of patients (177, 178). However, these effects were accompanied by SAEs, including cytomegalovirus reactivation and severe infections, which is why a prophylaxis with valganciclovir and strict monitoring is recommended. In addition, the duration of the beneficial effects was short, thus requiring the continuous administration of alemtuzumab.

The same group reported on a long-term follow-up study of 12 patients with HES and chronic eosinophilic leukemia

treated with alemtuzumab. Alemtuzumab was found to be effective, as 10 of 12 patients (83%) achieved a complete hematologic response, including the elimination of disease-related symptoms (179).

Conclusion – Limited data suggest alemtuzumab to be a valuable treatment option for advanced HES that are refractory to standard therapy or biologicals targeting IL-5, but larger RCTs are necessary to conclude on the efficacy of alemtuzumab in HES.

IL-5: Mepolizumab (phase 2/3 completed). Based on small open-label studies (180), a multicenter double-blind RCT comprising 85 patients assessed the efficacy of mepolizumab in FIP1L1−PDGFRA-negative HES; this study showed that mepolizumab induced a significant steroid-sparing effect along with a sustained reduction (up to 12 weeks) in blood eosinophil counts (181).

An open-label extension study of the above-mentioned trial enrolling 78 patients investigated the long-term safety and efficacy of mepolizumab in HES over more than 5 years and demonstrated that mepolizumab could serve as a long-term, well-tolerated alternative to corticosteroid treatment in patients with FIP1L1−PDGFRA-negative, corticosteroid-responsive HES (182).

Another trial ($n = 63$) in lymphocytic variant HES, characterized by overproduction of IL-5 by Th2 cells, showed that administration of mepolizumab reduced corticosteroid use to a similar extent in lymphocytic and nonlymphocytic HES, although blood eosinophil counts were lowered more efficiently in patients with nonlymphocytic compared to lymphocytic HES (183).

Conclusion – Mepolizumab treatment exerted a substantial corticosteroid-sparing effect on patients with FIP1L1−PDGFRA-negative HES, thus reducing corticosteroid-related morbidity. Further, larger RCTs are necessary to determine the efficacy of mepolizumab in HES.

IL-5: Reslizumab (phase 2 completed). The safety and efficacy of reslizumab have been evaluated in a small open-label study on four patients with treatment-refractory HES, one of whom was subsequently found to have the FIP1L1−PDGFRA fusion gene (184). Two patients experienced a rapid decrease in blood eosinophil counts and marked improvement in clinical symptoms within 48 h after receiving a single IV dose of 1 mg/kg reslizumab. The treatment was well tolerated, but exacerbation of symptoms and eosinophilia above baseline levels occurred as drug levels waned off.

Conclusion – Anti-IL-5 therapy may be useful in the treatment of HES irrespective of the underlying etiology, although rebound eosinophilia and attenuation of the therapeutic response were observed following cessation of reslizumab. Randomized controlled trials are needed, evaluating the use of reslizumab in HES.

Eosinophilic esophagitis

IL-5: Benralizumab (under development). As benralizumab reduces blood eosinophil counts, it is conceivable to use benralizumab in HES, eosinophilic esophagitis (EoE), NP, and EGPA (50, 178).

IL-5: Mepolizumab (phase 2 completed). An open-label phase-1/2 safety and efficacy study of mepolizumab in four adult patients with EoE and longstanding dysphagia with esophageal strictures demonstrated a decrease in peripheral blood and esophageal eosinophilia upon treatment (185). All patients showed improved clinical outcomes, including decreased dysphagia and improved QoL.

Another RCT demonstrated that mepolizumab was able to reduce eosinophil counts in the esophagus by 54% in adults ($n = 11$) with EoE but reported only mild clinical improvement (186).

Two recent studies determined the efficacy of mepolizumab in children (total $n = 59$) with EoE and showed that mepolizumab reduced esophageal eosinophilic inflammation in these patients (187, 188).

Conclusion – Although clinical trials in patients with EoE treated with mepolizumab demonstrated a significant reduction in esophageal and peripheral blood eosinophils, overall clinical improvement was not significant. This may be due to the fact that mepolizumab does not affect mucosal mast cells (189). Better standardization of patient-reported outcomes and identification of responders are required in future RCTs assessing the efficacy of mepolizumab in EoE.

IL-5: Reslizumab (phase 2/3 completed). A phase-2 dose-ranging RCT ($n = 227$) of reslizumab in children and adolescents with EoE showed 67% reduction in esophageal eosinophilia after treatment. However, this reduction did not correlate with an improvement in symptoms that were similar following reslizumab and placebo (190).

Conclusion – Further studies are needed to evaluate whether reslizumab might benefit patient subgroups with EoE.

IL-13: QAX576 (phase 2 ongoing). Currently, a phase-2 RCT is investigating the safety and efficacy of QAX576 in the treatment of EoE (191). The results are not available yet.

Adverse events

This section lists the reported AEs of the herein discussed biologicals, excluding the biologicals where currently no information is available on safety, tolerability, and AEs. The biologicals are ordered alphabetically according to their target (cf. also Table 1). Percentages indicate reported frequencies of the AE, while numbers refer to patients with AE over total counts of patients treated with the biological. If not otherwise indicated, there is no significant difference between placebo and active drug.

CD2: Alefacept

Alefacept can cause injection site reaction, elevated serum levels of aminotransferases, lymphopenia, and rarely serious infections and allergic reactions (131, 132).

CD11a: Efalizumab

Due to its association with JC virus-induced progressive multifocal leukoencephalopathy, efalizumab was withdrawn from the market (135).

CD20: Rituximab

Adverse events with the use of rituximab include standard infusion reactions and progressive hypogammaglobulinemia (865/3200); rarely thrombocytopenia (27 cases) and noninfectious interstitial lung disease (0.3–1%); and very rarely psoriasiform skin eruptions (six cases), cutaneous vasculitis (three cases), Stevens–Johnson syndrome, and toxic epidermal necrolysis (both single cases) (192). There is an increased risk of liver failure when rituximab is used in patients with hepatitis B virus, both in active and in occult carriers (192).

CD25: Daclizumab

Overall, AEs were similar in the daclizumab group compared to placebo, although daclizumab caused more severe AEs, including (transient) lymphopenia, increased rate of infections (nasopharyngitis), elevated serum levels of aminotransferases and bilirubin, cutaneous rash, nausea, and rarely anaphylactic reactions (15).

CD52: Alemtuzumab

Adverse events following alemtuzumab in patients with HES comprised infusion reactions, fever (4/12), lymphopenia (11/12), increased risk of infection [including herpes zoster (1/12), and pneumonia (3/12)] or reactivation [especially cytomegalovirus (2/12)], skin rash (1/12), and very rarely Epstein–Barr virus-positive B-cell lymphoma (1/12) (179).

IgE: Omalizumab

Omalizumab is safe and well tolerated according to several RCTs and postmarketing surveillance. Adverse events were usually mild, such as injection site reaction and headache (especially in children), and also included pharyngitis. The risk of immediate anaphylactic reactions occurring within 2 h following injection of omalizumab has been estimated at 0.1–0.2% (124/57300) (193), which is rather low and may be due to omalizumab's failure to inhibit cross-linking of FcεR1 by cell-bound IgE or other mechanisms (4, 21). Furthermore, particular attention has been dedicated to the risk of parasitic infections, cancer, and cardiovascular and cerebrovascular diseases. As for parasitic infections, a modest, nonsignificant increase in infection with intestinal helminths was found in a population of patients at a high risk of intestinal helminth infection when treated with omalizumab (34/68; 50%) as compared to placebo (28/69; 41%) (194); the other concerns have not been confirmed so far (22, 195).

In combination with SIT (n = 221), omalizumab caused only few AEs, including injection site reaction (19/213), headache (3/113), gastrointestinal (3/113) and ear symptoms (2/113), and infections (1/113) (21, 29).

All above-mentioned AEs concern the use of omalizumab in patients with asthma and/or perennial allergic rhinitis.

IgE: Quilizumab

Quilizumab was well tolerated with the most frequent AEs—headache (2/15) in asthmatic patients and upper respiratory tract infections (7/24) in patients with allergic rhinitis—occurring at similar frequencies as with placebo (6).

IL-1: Anakinra

Adverse events under treatment with anakinra in patients with rheumatoid arthritis comprise elevated serum levels of aminotransferases (5/1295) (196), leukopenia (7/1295) (196), increased risk of serious infections (30/2062) (197), and very rarely psoriasiform skin eruptions (one case reported) (192).

IL-1: Canakinumab

Use of canakinumab in patients with urticarial vasculitis was well tolerated by the patients and did not cause any SAEs (0/10) (126).

IL-1: Rilonacept

An open-label study in eight patients with Schnitzler's syndrome reported a total of 13 AEs that were mild or moderate in severity and considered not related to rilonacept, including infections (3/8) and skin rash (5/8) (124). No SAEs (0/8) were noted in that study.

IL-4: Altrakincept

Altrakincept was well tolerated with no major AEs in comparison with placebo. Most frequent AEs in patients with asthma were headache (6/46), nausea (6/46), upper respiratory tract infection (5/46), and pain (5/46) (38).

IL-4: AMG-317

In a phase-2 RCT in patients with asthma (n = 294), a few AEs associated with AMG-317 treatment were noted, mainly pertaining to injection site reaction (73/217), while upper respiratory infection (30/217), viral gastroenteritis (6/217), urticaria (1/217), headache (21/217), and dizziness (5/217) were seen rarely (41).

IL-4: Dupilumab

Injection site reaction (15/52), nasopharyngitis (7/52), nausea (4/52), and headache (6/52) were observed more often with dupilumab compared to placebo in a phase-2 trial in asthmatic patients (n = 104) (42) and in a phase-1/2 trial in AD (total n = 207) (143). Furthermore, three cases of SAEs (3/

179) were noted, but none of these reactions were considered related to dupilumab.

IL-4: Pascolizumab

The development of pascolizumab was halted due to a lack of efficacy in patients with asthma (43).

IL-4: Pitrakinra

There were only a few AEs following administration of pitrakinra in asthmatic patients, mostly injection site reaction and discomfort (8/12) when pitrakinra was given SC (44). General discomfort (7/16) was also reported following nebulizer administration of pitrakinra (44, 45).

IL-5: Benralizumab

Overall, benralizumab was well tolerated in patients with asthma, showing only few AEs, including nasopharyngitis (12/44), increased creatine kinase (11/44), and reduced white blood cell counts (15/44) (48, 50).

IL-5: Mepolizumab

In patients with HES, the frequency of AEs was similar between mepolizumab and placebo (181). The most frequent AEs observed in these patients were fatigue (15/61), upper respiratory tract infection (15/61), cough (14/61), headache (11/61), dyspnea (11/61), and nausea (11/61). Most AEs were considered not related to the study drug (198, 199).

IL-5: Reslizumab

Following reslizumab in patients with asthma, AEs were noted in similar frequency as with placebo, including headache (2/53), fatigue (4/53), nasopharyngitis (11/53), and pharyngolaryngeal pain (3/53) (58).

IL-9: Enokizumab

In patients with asthma, enokizumab was found to be safe and AEs were similar in characteristic and frequency as in the placebo group. Adverse events included hyperglycemia (12/63), nasopharyngitis (6/27), injection site reaction (10/63), pharyngolaryngeal pain (11/56), and reduced lymphocyte counts (6/56) (60, 61).

IL-12/IL-23: Ustekinumab

Ustekinumab is in patients with psoriasis associated with headache (165/2138), fatigue (71/2138), pruritus (59/2138), back pain (60/2138), injection site reaction (81/2138), arthralgia (72/2138), and infections (571/2138), including nasopharyngitis (184/2138) and upper respiratory tract infections (121/2138) (200, 201). Rarely, ustekinumab is also linked to serious infections, including viral infections and herpes zoster (7/2138) (192, 201). A meta-analysis suggested there was no association of ustekinumab with serious cardiovascular events (192).

IL-13: Anrukinzumab (IMA-638) and IMA-026

Adverse events were comparable between placebo and active drug in patients with asthma (anrukinzumab, $n = 27$; IMA-026, $n = 29$) and included upper respiratory tract infections, injection site reaction, and pharyngolaryngeal pain (64). No SAEs were reported.

IL-13: CNTO-5825

Adverse events with CNTO-5825 in healthy and atopic subjects ($n = 48$ received CNTO-5825) were mild to moderate and included headache (8/48), back pain (3/48), nasopharyngitis (6/48), epistaxis (2/48), erythema (2/48), palpitations (2/48), and vomiting (2/48) (65).

IL-13: GSK679586

Overall, GSK679586 appeared to be safe and well tolerated in a phase-1 and phase-2 RCT in healthy subjects and patients with asthma (total $n = 144$ received GSK679586) (66, 67). Most frequent AEs included nasopharyngitis (17/144), headache (24/144), lethargy (6/144), and diarrhea (5/144). Three SAEs occurred during the study periods, of which one case of extended syncopal episode was considered not related, whereas one case of supraventricular extrasystoles and one case of lethargy were related to GSK679586 (66, 67).

IL-13: Lebrikizumab

In patients with asthma, lebrikizumab was not associated with AEs other than the ones also noted in the placebo group, except for musculoskeletal events (14/106) that appeared more frequently in the lebrikizumab group, such as arthralgia (3/106), back pain (1/106), pain in the extremities (2/106), myalgia (2/106), neck pain (0/106), and arthritis (1/106) (9).

IL-13: Tralokinumab

The most frequent AEs with the use of tralokinumab in patients with moderate-to-severe asthma were injection site reaction (10/146), increase in asthma symptoms or asthma exacerbation (16/146), headache (13/146), nasopharyngitis (10/146), diarrhea (5/146), urinary tract infections (6/146), and transient slight increase in blood eosinophil counts (4/146) (68). No SAEs were observed (10, 68).

IL-17: Brodalumab

In patients with psoriasis, more AEs were observed with brodalumab than with placebo (73). The most common AEs were nasopharyngitis (13/158), upper respiratory tract infection (13/158), arthralgia (7/158), and injection site reaction (9/158), as well as rarely SAEs, including neutropenia (2/158).

IL-17: Secukinumab

The most frequent AEs with the use of secukinumab in psoriasis were nasopharyngitis (69/337), upper respiratory tract infection (11/337), headache (25/337), and worsening of psoriasis (18/337) (202). Rare cases of leukopenia and grade 1 or 2 neutropenia (19/337) have also been observed (202).

OX40L: huMAb OX40L

huMAb OX40L was well tolerated in asthmatic patients (n = 28) and no SAEs were noted in a phase-2 trial, with AEs occurring more often in the placebo group in this study (76).

TNF: Adalimumab

Overall, adalimumab is safe and well tolerated. Adalimumab has been associated with standard infusion reactions (13% with adalimumab *vs* 7% in controls; ≥1/10, especially with the presence of ADAs), elevated serum levels of aminotransferases (<1/10 to ≥1/100), increased risk of severe infection (0.03 per patient-year; <1/10 to 1/100), including herpes zoster (<1/10 to ≥1/100) (203), high risk of reactivation of tuberculosis (<1/100 to ≥1/1000), and hematological cytopenias (leucopenia <1/10 to ≥1/100; anemia and thrombocytopenia <1/100 to ≥1/1000); rarely psoriasiform skin eruptions (<1/100 to ≥1/1000), cutaneous lupus, lupus-like syndrome (<1/1000 to ≥1/10 000), and other immunological syndromes (see AEs of infliximab); and very rarely thromboembolism (seven cases, especially with the presence of ADAs) and neurological AEs (<1/1000 to ≥1/10 000) (see AEs of infliximab), especially demyelinating central and peripheral neuropathies (192, 204).

TNF: Etanercept

The overall safety and tolerability profile of etanercept is very good. Adverse events of etanercept are similar to those of infliximab and adalimumab, with the exception that the risk of reactivation of tuberculosis (<1 : 1000) is lower for etanercept than for the anti-TNF mAbs, but still higher with etanercept than with rituximab or anakinra (192, 204).

TNF: Golimumab

Overall, golimumab is safe and well tolerated. In a multicenter phase-2 RCT enrolling patients (n = 309) with severe persistent asthma, golimumab was reported to cause an increased rate of SAEs (30.3%; 70/231), which is why that trial was stopped (81). Based on that RCT and the literature, AEs due to golimumab treatment include serious infections (<1/10 to ≥1/100) and a high risk of reactivation of tuberculosis (<1/100 to ≥1/1000) (81, 192). Furthermore, the phase-2 RCT reported asthma exacerbations (<1/10 to ≥1/100) and the occurrence of eight malignancies in the golimumab group, including breast cancer, B-cell lymphoma, malignant melanoma, cervical melanoma, renal cell carcinoma, colon cancer, and two cases of basal cell carcinoma (81), although it is unclear whether these malignancies were linked to golimumab (192, 204).

TNF: Infliximab

Overall, infliximab is well tolerated and safe. Adverse events associated with the use of infliximab comprise standard infusion reactions (<1/10 to ≥1/100, especially with the presence of ADAs), elevated serum levels of aminotransferases (<1/10 to ≥1/100), an increased risk of severe infection (<1/100 to ≥1/1000, including herpes zoster), a high risk of reactivation of tuberculosis (<1/100 to ≥1/1000), and hematological cytopenias (<1/100 to ≥1/1000); rarely psoriasiform skin eruptions (<1/10 000), cutaneous vasculitis (<1/1000 to ≥1/10 000), cutaneous lupus, lupus-like syndrome (<1/100 to ≥1/1000; 0.1–0.8%), interstitial lung disease (<1/1000 to ≥1/10 000; in some reports up to 1%), sarcoidosis, inflammatory ocular disease, and antiphospholipid syndrome; and very rarely renal vasculitis, autoimmune hepatitis (<1/1000 to ≥1/10 000), inflammatory myopathy, pulmonary vasculitis, central and peripheral nervous system vasculitis, induction of optic neuritis (<1/1000 to ≥1/10 000), Guillain–Barré syndrome (<1/1000 to ≥1/10 000), and demyelinating central and peripheral neuropathies (<1/1000 to ≥1/10 000) (192, 204).

TSLP: AMG-157

Adverse events in patients with asthma (n = 31) under treatment with AMG-157 were comparable to placebo, with no SAEs occurring (83).

Conclusions on AEs

As IgE and Th2 cytokines have been shown in preclinical models to play an important role in fighting parasites, it was suggested that biologicals targeting these molecules might increase the risk of parasitic infections. Overall, this concern has not been confirmed, although a slight—but in comparison with placebo insignificant—increase in risk of parasitic infections was noted with the use of omalizumab (22, 195). Notably, the trials have been conducted in regions with a low incidence of parasitic infections.

As for IL-5 blocking agents, these biologicals lead to a reduction in eosinophils and basophils and might thus favor an increased frequency of recurrent infections. Several lines of evidence suggest that a deficiency in eosinophils is not associated with any pathology, although this merits further observation (205).

Overall, biologicals targeting IgE or Th2 cytokines have proved to be well tolerated.

Adverse events occurring with biologicals targeting TNF have been well examined, especially in patients suffering from chronic inflammatory and autoimmune disorders rather than in allergic diseases. Overall, TNF antagonists are well tolerated and safe. Particular AEs associated with the use of TNF antagonists include an increased risk of severe infection

(including herpes zoster), a high risk of reactivation of tuberculosis, and hematological cytopenias (192).

Future research directions

By accepting that asthma, AD, and other allergic diseases are complex syndromes comprising several endotypes, we realize that the underlying immunological, cellular, and molecular mechanisms of these entities are probably very heterogeneous. This might also explain why some clinical trials assessing certain biologicals in allergic disorders may have been unsuccessful in the past because they were performed without any consideration of the endotype of a given disease. Thus, it becomes crucial to better define endotypes and to discover disease biomarkers.

As for biomarkers, serum periostin levels, nasal IL-5 concentrations, and blood and tissue eosinophil counts might serve as predictors of a positive response to biologic therapy. Thus, patients with high pretreatment periostin serum levels showed better responses to IL-13-targeting treatments (9, 68, 69). Likewise, subjects with NP and increased nasal IL-5 concentrations were more likely to respond favorably to IL-5-directed biological therapy (176). And, blood or tissue eosinophilia served as a predictor of favorable response to IL-4Rα-targeting biologicals, such as pitrakinra (45). Moreover, the same study suggested that a subgroup of patients with moderate-to-severe asthma and blood eosinophilia carrying a specific *IL4Ra* genotype (rs8832GG) were particularly responsive to treatment with pitrakinra (45).

Also, IgE levels might serve as a biomarker. In fact, allergen-specific IgE levels have long been used to gauge therapeutic responses to SIT and VIT. With the advent of several new anti-IgE mAbs currently undergoing phase-1/2 testing, including MEDI-4212, QGE031, and quilizumab, IgE-based pretreatment assessment might become useful. In comparison with omalizumab, some of these new biologicals have improved IgE-binding properties, which is why these anti-IgE therapeutics might be of special interest in patients with IgE levels higher than 700 IU/ml.

Another mechanism likely responsible for the ineffectiveness of certain biologicals is the large redundancy in the immune systems. Thus, different cytokines and cytokine receptors ensure similar immunological and inflammatory processes, which make use of a single biological insufficient for blocking the targeted inflammatory pathway. Consequently, effective treatment might require blocking of multiple targets by using two and more biologicals or by combining a biological with another nonbiological therapeutic. Furthermore, better understanding of the pathophysiology of allergic disorders will also help identifying the most critical mediators of allergic inflammation.

It is to be expected that in the future, the indication for a biological will depend on biomarkers, endotypes, and genetic characteristics, rather than on clinical disease entities and syndromes. In this process, it is also paramount to characterize and understand AEs that follow a particular biologic therapy. The integration of these elements will allow a more tailored approach in using these biological response modifiers that will increasingly replace traditional treatment algorithms.

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Author contributions

Onur Boyman, Cezmi A. Akdis and François Spertini initiated the project. Onur Boyman and Celine Kaegi collected the data and prepared the first and the final version of the manuscript. All authors read and worked on the manuscript.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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