New biological treatments for asthma and skin allergies

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Abstract

Allergies are typically endemic, complex and heterogeneous diseases with a high impact at quality of life. Mechanistically, type 2 immune responses involving eosinophil and basophil granulocytes, mast cells and humoral factors such as IgE are key drivers of allergic diseases, although not the only ones. Fighting allergic diseases knows three strategies: prevention, symptomatic and causative therapy. While remarkable progress was made in understanding molecular events in allergies as a prerequisite for effective prevention and desensitization, this review article focusses on the most efficient symptomatic treatments – that is using more and more specific antibodies neutralizing particular immune pathways. We highlight and classify recent and upcoming developments in the three prototype chronic allergic diseases allergic asthma, chronic spontaneous urticaria, and atopic eczema. In all three examples, biologics such as dupilumab or omalizumab become reliable and efficient therapeutic options. Finally, we give an outlook how a diagnostic and therapeutic workflow might look like in the near future for these three major burdens of society.

Key words

asthma, urticaria, atopic eczema, atopic dermatitis, biologics, treatment, endotype, stratification, skin allergy

The development of biological treatments that specifically block the action of cytokines either directly or via blocking or their receptor offers nowadays a broad spectrum of new and efficient treatment options for inflammatory diseases. For being applied in an optimal way, these new treatments demand an in-depth knowledge of disease pathology. During the last decades, profound research delivered comprehensive insights into the pathomechanisms of asthma and skin allergies. However, personalized treatment regimens are still hampered by the high heterogeneity in between patients. Within this review, we will give an overview on how mediators of type-2 inflammation derived from T helper (Th) 2 cells, type 2 innate lymphocyte cells (ILC2) and B cells are driving the pathology of asthma, chronic spontaneous urticarial (CSU) and atopic eczema (AE), we will discuss disease biomarkers and the attempts to define disease endotypes and we will summarize biological treatment options, already on the market or in development, targeting type-2 but also non-type inflammation.

Asthma

Current state of the art of definition and epidemiology

Asthma is a common chronic and heterogeneous condition affecting more than 300 million people worldwide [1], with a varying prevalence (i.e. from 21% in Australia to 0,2% in China) [2,3]. Variation also exists between genders; in children, boys are most affected but that changes at puberty to a higher prevalence in women (around 20%) [4].

Asthma has a high social impact, mainly in low- and middle-income countries, where years of life lost due to asthma are increasing [2]. The economic burden of asthma is estimated to exceed the combined burden of tuberculosis and HIV/AIDS [5].

Pathogenesis

Inflammation represents a key feature of asthma pathogenesis, with a variety of host/environment interactions that are diverse in time and tissue[2] leading to its complexity and its heterogeneity. Studying this heterogeneity led to the understanding that asthma represents

more a syndrome than a single disease[6]. The syndrome asthma describes many different phenotypes (observable characteristics) that may have different underlying pathogenic mechanisms (i.e. asthma endotypes).The era of personalized medicine in asthma demands a deeper understanding of these phenotypes and their underlying endotypes[7] to assign the most appropriate therapy to each patient.

The first described asthma phenotypes were 'intrinsic' and 'extrinsic', which correspond to the later and for many decades dominant categories of non-allergic and allergic asthma[8].

The identification of different T helper (Th) subsets[9], followed by identification of a Th2-like dominated inflammation in the airways of patients with allergic asthma[10] framed allergy and asthma research to investigate this pathway in depth[11-14] and resulted in the establishment of the first endotype paradigm in asthma, the Th2 and the non-Th2 endotype[15].

The Th2-type included mainly the classical allergic asthma, characterized by the presence of serum immunoglobulin E (IgE) antibodies and/or a positive skin-prick test to allergens and was mostly observed in children, while the non-Th2 type was less allergic and mainly attributed to adults. Indeed, 50–70% of asthma patients are allergic and include mostly children (especially those with severe asthma). In allergic individuals, the uptake of allergens in the airways by dendritic cells initiates a cell-mediated immune response, leading to expansion of Th2 cells that secrete pro-allergic cytokines such as interleukins (IL)-4, -5, -9 and -13. IL-4 has a key role in B cell isotype switching and IgE synthesis. IgE in turn binds to high affinity receptors on mast cells and induces their activation after allergen mediated crosslinking of membrane-bound IgE molecules. Activation of mast cell leads to their degranulation and immediate release of stored mediators, i.e. histamine, tryptase and heparin, as well as *de novo* synthesis of several lipid mediators including prostaglandins and leukotrienes that induce bronchoconstriction[16]. IL-5 is essential for maturation and survival of eosinophils[13,17]. IL-9 mediates mast cell and eosinophil accumulation, airway hyperresponsiveness and mucus production[13,17,18]. IL13 plays an important role in airway bronchial hyperreactivity, goblet-cell metaplasia and mucus production as well as in fibrosis[19].

The Th2/ non-Th2 endotype paradigm was challenged by the fact that patients with eosinophilic inflammation but without allergic sensitization exist. This challenge could be explained by the recent discovery of innate lymphoid type 2 cells (ILC2) cells[20] that differentiate from progenitor cells in presence of so called *alarmins* such as thymic stromal lymphopoietin (TSLP), IL-33 and IL-25[2] and release IL-4, IL-5 and IL-13. These findings required an adaptation of the initial endotype paradigm that is now more generally named as type-2 high, including Th2-and ILC2-driven inflammation, and the type-2 low endotype[21]. The type-2 high endotype is present in about 50% of adults with asthma (Figure 1).

In the low type-2 asthma, neutrophils dominate the infiltrate and inflammation is driven by Th1, Th17 and ILC3 cells that release IL-17 and activate macrophages that in turn release CXCL8, a key chemoattractant for neutrophils[2]. Mixed phenotypes with both eosinophils and neutrophils or even paucigranulocytic with few inflammatory cells exist but are less understood.

Current indication for biologic therapy of asthma.

Long-term treatment goals are to achieve symptom control and to minimize the risk of future exacerbation, fixed airflow limitation and side effects of treatment[22]. A comprehensive approach includes nonpharmacological measures, i.e. avoidance of triggers and a stepwise approach (steps 1–5) with increasing doses of medications, primarily ICS, often in combination with a second controller, starting with a β_2 agonist and eventually adding leukotriene receptor antagonists or theophylline (for adults) before the use of systemic corticosteroids[22]. Inhalation technique control and assessments of comorbidities are also key factors in asthma treatment. Around 5% of patients need escalation to step 5, the use of systemic steroids, and may even then remain uncontrolled which defines them as patients with severe asthma according to ERS/ATS criteria[23]. For those patients, biologic therapy is indicated[24]. Current targets for type 2 asthma are IgE (Omalizumab), IL-5 (Mepolizumab and Reslizumab), IL-5Ra (Benralizumab), and IL-4Ra (Dupilumab) (Table 1).

Omalizumab, a humanized, monoclonal antibody (mAb) directed against IgE, was the first biologic-based therapy, available in clinical settings in the early 2000s. It is licensed for

moderate to severe allergic asthma in patients ≥ 6 years old with IgE higher than 30 IU/L. Omalizumab prevents IgE from binding to its high-affinity receptor (FcεRI), which is present on mast cells and basophils, blocking their allergic response. It also downregulates the expression of high-affinity IgE receptors on mast cells[25]. Several randomized control trials (RCTs) and real-life studies[26] have shown that Omalizumab reduces asthma exacerbation (by about 25%) and hospital admissions in both children and adults[25]. Omalizumab reduces also virus-associated exacerbations[27], possibly by increasing the anti-viral response and IFN-α production from dendritic cells[28]. Omalizumab is well tolerated with a low risk (0.1–0.2) of anaphylaxis [29].

Mepolizumab and Reslizumab are both mAb that bind to IL-5 preventing it from binding to its receptor[30]. They are licensed for patients with severe asthma and high blood eosinophils (≥ 150 cells/μL for Mepolizumab, ≥ 400 cells/μL for Reslizumab).

Mepolizumab has been shown to reduce asthma exacerbation by about 50%, with a small improvement in lung function (FEV1 increase in 110 ml) and QoL[31]. In patients with OCS-dependent asthma, Mepolizumab reduces its dosage by 50% in parallel with a reduction of exacerbation and with no loss of asthma control [26,32]. Mepolizumab has a safety profile similar to placebo.

Reslizumab reduces asthma exacerbations similar to Mepolizumab and improves FEV1 within 4 weeks when blood eosinophils are ≥ 400 cells/μL; it also results in an improved QoL[31,33]. Reslizumab is the only intravenous mAb, and its dose is weight based. Reslizumab is well tolerated with adverse effects similar to a placebo, although three cases of anaphylaxis have been reported[34].

Benralizumab is directed against IL-5Ra. Due to its afucosylation, Benralizumab interacts with the FcγRIIIa receptor in natural killer (NK) cells to induce an antibody-dependent, cell-mediated cytotoxicity (ADCC), resulting in rapid depletion of eosinophils[35]. It reduces significant asthma exacerbations at a level similar to other anti-IL-5 biologics, especially in patients with blood eosinophils ≥ 300 cells/μL. Benralizumab has also an oral steroids-sparing effect together with

exacerbation reduction by 70%[36]. Benralizumab is well tolerated, but hypersensitivity reactions have been detected including anaphylaxis, angioedema and urticaria.

Dupilumab targets the IL-4 receptor alpha and blocks the signalling of both IL-4 and IL-13. It has been tested in moderate to severe asthmatics, reducing asthma exacerbations by approximately 50% and significantly improving lung function (FEV1) within 2 weeks in patients with elevated type 2 biomarkers (blood eosinophils ≥ 150 cells/μL and FeNO ≥ 25)[37]. In patients with steroid-dependent asthma, Dupilumab reduced OCS use by 70%, accompanied by a 60% reduction in exacerbation and improved lung function[38]. Dupilumab has a favourable safety profile, with side effects of injection-site reaction and transient blood eosinophilia.

Although the main outcome in the above mentioned clinical trials was reducing asthma exacerbations, hospital admissions as wells as oral-steroid sparing, other important clinical outcomes such as lung function are not conclusive, yet. Omalizumab has shown minimal or equivocal improvement in lung function[39]. In the anti-IL5/5Ra antibody family, a recent Cochrane review found a small but significant improvement in mean pre-bronchodilator FEV1 of between 0.08L and 0.11 L[31]. A Dupilumab phase III study has shown an increase of FEV1 up to 0.32 L at 12 weeks[37]. These studies highlight that future real-time studies are needed to evaluate the effect of biologics in lung function decline.

All above mentioned biologics have a good safety profile. However, as they all interfere with the immune system and patients will receive them for a long period of time, we should be aware of any potential long-term immunomodulatory effects. The longest data exist for anti-IgE treatment without any concerns until now. No data exist for anti-IL5/5Ra and for anti-IL-4Ra, yet. Here, biologic function of these targets should be kept in mind. Eosinophils, for example, are considered diverse cells[30] that do not only function as effector cells but are also involved in tissue homeostasis and, therefore, have a much broader role in allergic inflammation and helminth infections than assumed so far[30,40].

Selecting the biologic for severe uncontrolled asthma

Choosing the most appropriate biologic treatment is challenging[7,39,41]. Confirming asthma severity, re-establishment of asthma diagnosis, comorbidities and patient adherence is essential before initiating a biologic therapy.

With the available biologics, the choice has to be made between anti-IgE, anti-IL5/5Ra and anti-IL4Ra. As there are no RCT studies directly comparing those biologics, the patient phenotype and endotype has to be assessed as best as possible to achieve the expected efficacy and safety of the treatment. Thus, the first step is to define the occurrence of type 2 or non-type 2 asthma and subsequently to characterize the underlying sub-endotype: allergic-predominant, eosinophilic-predominant, or AHR (smooth-muscle contraction and hyperresponsiveness) and mucus predominant.

In patients with an allergic-predominant phenotype, i.e. early onset asthma, history of allergies and/or clinically significant SPT/RAST, IgE > 100 IU/mL, co-existence of allergic rhinitis, moderate high FeNO (i.e. Up to 50 ppd) and low number of blood eosinophils (<300 cells/µL), Omalizumab could be considered as the first choice due to its proven efficacy and safety. In patients with eosinophil-predominant asthma, i.e. late onset asthma, no history of allergy or clinical significant SPT/RAST and normal IgE and high blood eosinophils, ≥ 300/µL, an anti-IL5/5Ra should be the first choice.

In patients with characteristics from both sub-endotypes showing an allergic/eosinophilic overlap, either anti-IgE or an anti-IL5/5Ra could be a possible choice. Anti-IgE has been shown efficient even in patients with blood eosinophils ≥ 300/µL at 16 weeks[42] and has a documented long time safety profile, even during pregnancy [43]. There is a documented strategy for evaluating the effectiveness of anti-IgE therapy after 16 weeks, while responsive data for an anti-IL-5/5Ra treatment are still lacking[44]. As anti-IL-5 treatment can be effective in patients that have been previously treated with anti-IgE, evaluation of therapeutic efficacy of anti-IgE after 16 weeks seems to be reasonable to decide if the patient should continue or switch to anti IL5/IL5Ra[45]. However, studies evaluating switching from anti-IgE, or anti IL-5/5Ra to anti IL-4Ra are not available, yet.

High blood eosinophils and a history of exacerbations predict an enhanced response to all three anti-IL5 mAbs, which all show a similar reduction in asthma exacerbations. Thus, decision for therapy is made according to blood eosinophil levels, co-existence of nasal polyps[46] and weight as predictors for treatment success.

Patients with broader clinical signs and symptoms which could be ascribed to IL-4 and IL-13 (goblet-cell hyperplasia, mucus secretion, smooth-muscle contraction and hyperresponsiveness together with eosinophil recruitment) could especially benefit from Dupilumab therapy[39,47].

Future targeted treatment

There is an increased interest in developing future targeted therapies, mainly for type 2 inflammation. Focus has been given to alarmins. Even if those epithelial-cell-derived cytokines can be induced by several stimuli, including environmental and microbial triggers, their key role in inducing Th2 and ILC2 cells has rendered them promising targets for the treatment of type 2 inflammation. Tezepelumab, an mAb targeting TSLP, decreased asthma exacerbations in patients with moderate asthma unrelated to blood eosinophils and FeNO[48]. A treatment targeting IL-33, either directly (IL-33) or via its receptor (anti-ST2), is also in clinical development.

An interesting novel approach is to optimize airway delivery of mAbs. Currently, a nebulized biologic therapy approach targeting IL-13 is under development in animal models[49].

Development of biomarkers to identify suitable patients and predict and monitor their response to biologics [50] is, however, the most crucial task for the future.

Definition of skin allergies

Biologics are highly efficient and cost-intense therapies. Thus, they are generally only justified in severe and chronic diseases. Concerning skin diseases, occasionally self-limited skin allergies are treated with biologics. Namely, severe cases of drug-induced exanthema such as toxic epidermal necrolysis might be treated with a single injection of anti-TNF-α as early at

onset as possible [51]. However, allergic skin rashes such as allergic contact dermatitis (ACD) or drug exanthema are self-limited as soon as the trigger is removed and are usually not treated with biologics. Thus, skin allergies are defined here as chronic inflammatory conditions that are mediated by and/or associated with immediate and/or cytotoxic hypersensitivity reactions.

Chronic spontaneous urticaria

Chronic spontaneous urticaria (CSU) is a common disease with a prevalence of up to 1%[52]. CSU is characterized by the recurrent spontaneous appearance of itchy wheals, angioedema, or both for more than 6 weeks[53]. Patients affected by CSU are often dramatically impaired in their quality of life, which is why consequent implementation of current treatment guidelines as well as development of new and better therapies is necessary.

Pathogenesis

Signs and symptoms of urticaria are mainly caused by the activation of mast cells (MC) and the subsequent release of histamine. The exact mechanisms leading to activation of MC in chronic urticaria patients are, as of yet, not fully characterized. There is, however, strong indication that autoimmunity, either, “autoallergic” (type I, with IgE antibodies to local autoallergens), or “autoimmune” (type IIb ,with IgG autoantibodies to IgE or its receptor), is the most frequent cause of CSU[54] (Figure 2). While in patients with autoallergic or autoimmune CSU, the respective autoantibodies are required for MC degranulation, there are many co-factors that can be involved in modulating the activation status of MC, for example pseudoallergens, neuropeptides or bacterial products. Furthermore, in addition to MC, eosinophils, basophils and neutrophils are thought to contribute to the pathogenesis of CSU by migrating from the circulation into the skin at sites of MC degranulation, resulting in blood basopenia and cellular skin infiltration[55,56]. It is, as of yet, unclear how this mild leukocytic infiltrate contributes to CSU pathogenesis. Possibly, the inflammatory environment also modulates the activation threshold of MC.

Guideline-recommended treatment algorithm

An effective treatment for CSU patients should always aim for complete control of symptoms. To achieve this, urticarial symptoms and the burden of the patients need to be assessed continuously before and during treatment. To do so, validated scores and questionnaires are recommended, for example the Urticaria Activity Score (UAS), the Chronic Urticaria Questionnaire for the Quality of Life (CU-Q_2oL) and the Urticaria Control Test (UCT)[53]. If CSU is not sufficiently controlled, for example if the patient has a UCT score of less than 12, treatment escalation should be performed as recommended by the current guidelines[53]. The standard treatment of CSU are second-generation antihistamines in standard, i.e. once daily, dosing. In case of inadequate control, antihistamines dosing should be increased after 2-4 weeks or earlier, if symptoms are intolerable, to up to four times the standard dose. However, many patients still suffer from urticaria despite proper antihistamine treatment. In these patients, the guideline recommends as next step the addition of Omalizumab. Omalizumab is currently the only licensed drug for the treatment of patients who are not controlled by a standard dosed antihistamine. For those patients who also fail to respond to Omalizumab, the current guidelines recommend cyclosporine treatment after six months of Omalizumab treatment weeks or earlier, if symptoms are intolerable[53].

Proposed mechanism of action of Omalizumab

In autoallergic CSU, IgE against autoantigens is thought to be the relevant factor responsible for MC activation and thus for the elicitation of urticarial symptoms. Different groups have recently identified functional" i.e. MC degranulating" IgE against autoantigens such as thyroid peroxidase[57] or IL-24[58] and in a large proportion of CSU patients higher than normal levels of IgE are detected[59], with the majority of the total IgE being autoreactive[60]. Furthermore, specific and functional IgE against staphylococcal enterotoxins has been identified in many CSU patients[61]. In those patients where IgE is responsible for the degranulation of MC, the elimination of IgE by anti-IgE antibodies will result in cessation of symptoms, typically within the first days or weeks after the first injection.

There are, however, CSU patients who poorly respond to Omalizumab or who show a late onset of symptom improvement, i.e. within months. These patients typically have low levels of total IgE, low basophil FcεRI expression and are positive in the basophil activation tests[62-64]. In these patients, the effects of Omalizumab are thought to be mediated via the down regulation of FcεRI on skin MC, which has been shown to occur within three months after start of Omalizumab treatment[56].

While the above described mechanisms of action are likely to be the most relevant in most CSU patients, there may be subgroups of patients in which other mechanisms are relevant and where Omalizumab is effective via different actions. For example, other proposed mechanisms of action of Omalizumab include the ability of Omalizumab to change mast cell releasability and to affect the coagulation cascade[65]. Further ongoing research is aimed at fully characterizing all potential mechanisms of action of anti-IgE efficacy in CSU.

Biologics under investigation

In 2014, Omalizumab has been licensed for the treatment of patients with antihistamine-refractory CSU. Since then, additional randomized controlled trials with Omalizumab have been conducted in three forms of inducible urticaria, cholinergic urticaria[66], cold urticaria[67] and symptomatic dermographism[68], all showing the potential of an effective anti-IgE treatment in inducible urticaria.

In CSU, first results of a randomized, double-blind, placebo- and comparator-controlled phase 2b trial with Ligelizumab have been presented at the EAACI 2018. Ligelizumab is a humanized monoclonal IgG1 antibody that binds, similar to Omalizumab, to the Cε3 domain of IgE. The *in vitro* affinity of Ligelizumab is about 50-fold higher than that of Omalizumab and allergen skin prick tests have shown much higher potency of Ligelizumab *in vivo* as compared to Omalizumab [69,70]. In this study, more patients treated with Ligelizumab 72 and 240mg achieved complete control of CSU symptoms as compared with to patients treated with Omalizumab and placebo[71]. Based on these positive results, there are ongoing phase 3 trials investigating the efficacy and safety of Ligelizumab in CSU patients refractory to antihistamine treatment.

Based on the hypothesis that autoreactive antibodies are responsible for symptoms in CSU, a depletion of antibody producing B cells could be beneficial in CSU patients. Quilizumab, a humanized monoclonal antibody that targets the M1 prime segment of membrane expressed IgE, has been investigated in a randomized, placebo-controlled phase 2 trial in CSU. The proposed mechanism of Quilizumab is the specific reduction of IgE levels by causing the depletion of IgE-switched B cells and plasmablasts. The study, however, failed to reach the primary endpoint in comparison to placebo. This was most likely due to an only moderate reduction of IgE by ~30% until week 20[72].

Rituximab, a chimeric monoclonal anti-CD20 antibody, depletes memory B cells that are necessary for autoantibody production. Overall, five individual case reports have been published, four of which have shown efficacy with a sustained response[73]. So far, there is no published controlled trial on the efficacy of Rituximab in CSU, a trial registered on clinicaltrials.gov (NCT00216762) has been halted by the FDA due to safety concerns.

Future developments

There are currently two ongoing clinical trials with biologics assessing the proof of concept for the use in CSU. In a first pilot study, the efficacy of AK002, a humanized monoclonal antibody directed against Siglec-8, is assessed in patients with antihistamine-resistant CSU (NCT03436797). Siglec-8 is expressed by eosinophils and mast cells and activation of Siglec-8 is thought to induce inhibition or depletion of these cells, which would make it ideally suited for the treatment MC-related diseases such as CSU[74]. As of yet, there are no published results of the trial available. In another multi-center, randomized, placebo-controlled trial, Dupilumab, a monoclonal anti-IL-4Rα antibody, is assessed for its efficacy and safety in patients with CSU (NCT03749135). While the trial is ongoing and results are not expected in the near future, a recently published case series of treatment refractory CSU patients has shown efficacy of Dupilumab in six patients[75].

Anti-TNF antibodies are widely used in dermatology, both in in-label indications such as psoriasis as well as in off-label indications. Regarding the efficacy of TNF-a antibodies in the

treatment of CSU, there is only limited information available. A case series that retrospectively analyzed 25 patients with CSU treated with Etanercept or Adalimumab, reported a beneficial response in 15 (60%) of the patients[76].

Similar to TNF, the potential pathogenetic mechanisms involving IL-5 in CSU are currently unclear. There are, however, two single case reports showing that anti-IL-5 treatment using Mepolizumab[77] or Reslizumab[78] can be beneficial in CSU. According to clinicaltrials.gov, a single blind, non-randomized trial is currently performed to assess the efficacy of Benralizumab in CSU (NCT03183024).

Atopic eczema

Atopic eczema (AE) or atopic dermatitis is the disease with the highest burden of all skin conditions throughout life[79]. In fact, AE impacts the quality of life to a similar degree as epilepsy or diabetes in children or cancer in adults[80,81]. AE is very common, reaching a prevalence of up to 30% of all children and 3% of adults in the Western population[81]. Its complex pathogenesis involves a genetic predisposition and environmental factors and leads to the triade of dry skin, itch, and cutaneous inflammation[82] (Figure 3).

Are allergies relevant for the pathogenesis of AE?

AE might develop independent of skin allergies and be mediated by non-type 2 inflammation[83], but in 80% of the cases specific sensitizations to aeroallergens or food are identified. Especially in children, food allergens might be the major trigger of AE[84], while in later life usually sensitizations to aeroallergens such as birch (Bet v 1) are common. These sensitizations might then cause cross-reactivity to food, e.g. apples and other fruits[85]. However, the relevance of allergies for AE is not entirely clarified. Of particular importance here is the role for specific immunotherapy. While some studies suggest a positive effect for AE, there is conflicting evidence whether desensitization might influence AE in a positive way[86]. Ongoing and future efforts will need to determine which subgroups or endotypes of AE might benefit best[87,88]. Also

in case of allergic contact dermatitis (ACD), evidence is conflictive regarding the impact on the course of AE[89]. Depending on the eliciting hapten, ACD reactions might even be less frequent and attenuated in AD patients[90]. This inconsistency is probably related to the fact that haptens drive distinct immune responses[91] that might reinforce the type 2 immunity of AE or not – the first is the case for fragrances, the latter for Th1/Th17 skewing haptens such as nickel, imiquimod[92], or DNCB. In line with this, AE patients were reported to generally develop a Th2-skewed ACD reaction[93]. Thus, reactions to nickel might be less frequent or attenuated as compared to the general population, while ACD to fragrances might be more frequent in AE. Finally, the Atopy Patch Test (APT) identifies AE patients that develop eczematous lesions to aeroallergens [94]. Confirming the relevance for the APT, a subgroup of AE patients has been shown to react with skin exacerbation upon pollen challenge[95]. Thus, skin allergies are relevant at least in a subgroup of AE.

Current biologic therapy of AE

European guidelines for the treatment of AE recommend a step-wise approach[88,94]: avoiding triggers and basic treatment of the barrier is recommended in all stages of the disease. In moderate forms, AE should be treated early and hard with topical steroids and in remission with a pro-active therapy; severe forms might be treated with cyclosporine, methotrexate, azathioprine, or mycophenolate-mofetil. However, all these therapies are of limited effectiveness and have long-term side effects. Thus, identifying specific and effective biologics for the treatment of AE was and still is a great unmet medical need. As this review article focusses on biologics, promising small molecules such as JAK inhibitors[96] will not be discussed. Studies investigating biologics in AE treatment follow three general strategies (Table 1): adapting biologics approved for other skin diseases such as psoriasis for AE, most of them targeting non-type 2 pathways such as type 3 (Th17) immunity; biologics dampening acute phase reactions, e.g. IL-6 or IL-1b; and finally, biologics neutralising type 2 (Th2) immunity.

In line with the classification of inflammatory skin diseases according to their immune response patterns [97], biologics highly efficient for psoriasis (type 3 according to[97]) fail to proof efficacy in AE (type 2a according to[97]). TNF inhibitors have been investigated in several case series with no convincing overall efficacy[98]. Investigation of Ustekinumab in a placebo controlled trial resulted in SCORAD50 response at 16 weeks in 31% of the patients receiving verum as opposed to 19% in the placebo group[99]. Due to the cross-over design, long-term effects could hardly be assigned to Ustekinumab. Thus, it cannot be excluded there is a subset if AE that might benefit from these substances, but overall psoriasis biologics are not suitable for treating AE.

Biologics neutralizing acute phase substances such as IL-6 have also been investigated in the past for AE. However, there is very limited evidence, e.g. a case series of three patients treated with Tocilizumab with good response, but development of side effects[100]. In summary, there is the trend to modify innate and acute phase responses in AE; however, this trend is currently proceeded rather by investigating small molecules than antibodies.

Finally, a major breakthrough in treating AE was achieved by neutralizing type 2 immunity. An early small study investigated the IL-5 antibody Mepolizumab. Here, 4 out of 20 patients showed a PGA reduction, but there was no significant difference between the active drug and placebo groups at 14 days regarding SCORAD or CCL17 serum levels[101]. The study was underpowered and too short, but still leaves room for speculations that a subgroup of AE patients might respond to neutralizing IL-5. Similarly, conflicting and way too few evidence exists regarding humoral factors of type 2 immunity as targets for AE treatment. A case series of AE patients treated with Rituximab reported a good outcome in all 6 investigated patients after 24 weeks, with a mean reduction on EASI from 29 to 8[102] or in severe childhood AE[103]; however, there are also negative reports[104,105]. More evidence exists regarding Omalizumab, where the initial study in 21 patients with co-existing asthma and AE reported a SCORAD50 response in all 21 patients[106]; follow-up studies showed a more heterogeneous picture, with a responder rate of 5-30% of AE patients[107-110]. The response to Omalizumab was independent

of circulating IgE levels, thus biomarkers guiding therapeutic decision for Rituximab or Omalizumab are amiss.

The first breakthrough in AE therapy was achieved by the IL-4 receptor alpha antibody Dupilumab. As a consequence of several phase III studies showing an EASI75 response in >50% as monotherapy[111] and >65% in combination with topical steroids[112], Dupilumab was approved for moderate to severe AE in the US and Europe in 2017. Dupilumab also efficiently reduces pruritus and improves quality of life. Its safety profile is very high, with the exception of conjunctivitis that occurs in roughly 10% of AE patients and that requires special attention in this population[113].

Future developments: focussing on type 2 immunity and epithelial cytokines

Besides Dupilumab, there are two more biologics interfering with the type 2 cytokine IL-13, namely Lebrikizumab and Tralokinumab (Figure 4). In a phase II study with 209 patients assessing lebrikizumab that allowed concomitant topical steroids, 82% achieved an EASI50 response with 62% placebo responders[114]. Tralokinumab showed good efficacy in phase II, with a dose-dependend mean EASI improvement by 15 points[115]. Neutralizing the type 2 cytokine IL-31 that is a central mediator of itch markedly reduced pruritus in two phase II studies, but had only moderate effects at EASI scores[116,117].

Targeting epithelial cytokines such as IL-17C and Fezakinumab (IL-22 antibody) or IL-22R are at early stages of development. There is clear evidence that AE is a heterogeneous disease, probably comprising several endotypes[118]. Comparisons of childhood versus adult AE or European versus Asian AE endotypes[119] gives evidence that the classification of AE is not precise enough for the currently available highly specific biologics. Molecular classifiers are at the step of clinical validation[120-122], but reliable biomarkers predicting clinical outcome of a therapy are very scarce. One recently suggested biomarker is the cutaneous level of IL-22 that predicts clinical response to Fezakinumab, an antibody neutralizing IL-22 with an overall moderate efficacy[123]. Thus, endotypes and biomarkers are prerequisites for the next breakthrough in AE therapy[83].

Summary and outlook: a diagnostic and therapeutic workflow for allergic diseases

Chronic inflammatory diseases usually involve adaptive immunity and epithelial cells andcan be grouped according to their immune response pattern. Here, AE is for instance assigned to a pattern containing eczematous and blistering diseases that are all mediated by type 2 inflammation[97]. The most promising biologics to treat allergic asthma and skin allergies - either already licensed or in development - neutralize the type 2 immunity (Figure 4). However, asthma and skin allergy patients show a heterogeneous degree of response and there is a substantial number of non-responders in all available or foreseen biologics.

Remarkable advances defined endotypes of asthma[7] and urticaria[53] according to their pathogenesis as well as therapeutic response; in AE, initial progress is made in understanding how distinct clinical entities and species might be linked to molecular events[83]. The ideal future treatment algorithm of asthma and skin allergies needs to take into account these endotypes and would involve prevention, symptomatic and causative therapies (Figure 5). To achieve this aim, molecular diagnostics needs to improve. Currently, the greatest obstacle on the way to precision medicine in the field is the gap between advances in understanding pathogenesis and availability of specific therapies at the one hand side and missing predictive biomarkers and precise diagnostics at the other side.

Figure legends

Figure 1: A simplistic overview of asthma pathogenesis and the current biologics that target pathogenic mediators. CRTh2: chemoattractant receptor – homologous molecule expressed on Th2 cells, ILC2: innate lymphoid cell type 2

Figure 2: Potential targets in the treatment of chronic urticaria. Baso: basophil, CRTH: chemoattractant receptor-homologous molecule expressed on Th2 cells (DP2), Eos: eosinophil, H1/4R: histamine 1/4 receptor, NK: neurokinin, C5: complement 5, Ig: immunoglobulin, IL: interleukin, LTR: leukotriene receptor, PI3K: Phosphoinositide 3-kinase, S1P: sphingosine-1-phosphate, SHIP: SH2-containing inositol phosphatase 1, Syk: spleen tyrosine kinase, TSLP: thymic stromal lymphopoietin

[1]currently available, [2]under investigation, [3]hypothetical

Figure 3: Pathogenesis of atopic eczema. The pathogenesis of AE is represented by a vicious circle of barrier damage and immune dysbalance. Therefore, the initial starting point is difficult to define. For explaining this figure, we will start with an already disrupted epithelial barrier that allows penetration of environmental allergens. These allergens are shuttled by antigen-presenting cells (APC) to the regional lymphnodes and presented to naïve T cells that in presence of e.g. thymic stromal lymphopoietin (TSLP) differentiate into allergen-specific T helper (Th) 2 cells and are attracted back to the skin, the site of allergen penetrance. Production of type 2 cytokines such as IL-4, IL-13 and IL-5 lead to further barrier damage by down-regulation of Filaggrin and recruitment of eosinophils. Subsequently, deep parts of the skin are colonized with bacteria such as *Staphylococcus aureus* (*S. aureus*). *S. aureus* in turn produce superantigens that activate T cells in and allergen independent manner. In addition, inflammatory dendritic epidermal cells (IDEC) recognize allergen by membrane-bound IgE produce proinflammatory cytokines and induce differentiation of Th1 cells which marks the transition from an initial type-2 dominated immune response towards a mixed type-2/type-1

(IFN-g)/type-17 (IL-17, IL-22) response. In presence of type 2 cytokines, the anti-microbial effects of type 17 cytokines are drastically diminished leading to constant bacterial colonization of the skin. Tissue damage that is induced by inflammation does not only enhance barrier damage but also opens the risk for auto-inflammatory processes.

Figure 4: Mode of action of Type 2 immunity targeting biologics. APC: antigen presenting cell, TSLP: thymic stromal lymphopoietin

Figure 5: Toolbox to a tailored diagnostic and therapeutic approach in heterogeneous allergy patient populations.

Precision medicine with a tailored therapy is hampered by the heterogeneous profile of Asthma, CSU and AE patients combined with their complex pathogenesis. To achieve precision medicine, individual diagnostic measures taken from a toolbox of available diagnostics have to be consecutively combined with individualized treatment regimens. Prerequisite of such an algorithm, however, are biomarkers that reliably distinguish disease endotypes and resolve the heterogeneous patient collective. The colour code of each individual indicates which diagnostic tool and which subsequent therapy would be optimal for this single person.

Tables

Table 1. Biologics available and in clinical trials for asthma and skin allergies

Table 2. Textbox: Milestones achieved for asthma

Table 3. Textbox: Milestones achieved for CSU

Table 4. Textbox: Milestones achieved for AE

	Status and efficacy in				
	Drug	**Target**	**AE**	**Asthma**	**Urticaria**
Type 17 immunity	**Ustekinumab**	IL-12p40 (IL-12 and IL-23)	off-label not effective [99]	-	off-label
	Etanercept	TNF-α	off-label contradictory/ not effective	TNF-α inhibitors are no longer under development due to an increased rate of SAEs of Golimumab in phase II	off-label case reports [76]
	Adalimumab	TNF-α	-		off-label case reports [76]
	Infliximab	TNF-α	off-label potentially effective with TCS co-therapy[98]		-
Innate immunity	**Anakinra**	IL-1	off-label	-	off-label
	Tocilizumab	IL-6R	off-label case reports [100]	-	off-label
	Bermekimab	IL-1a	Phase II (NCT0349674) dose dependent effects	-	-
Type 2 immunity	**Duplimab**	IL-4Ra	approved	approved	Phase II (NCT03749135) [75]
	Mepolizumab	IL-5	off-label no long term studies available [101]	approved	off-label case reports [77]
	Resilizumab	IL-5	-	~50% improvement [31,33,124]	-
	Benralizumab	IL-5Ra	Phase II (NCT03563066) recruiting	~50% improvement [125]	conflicting results
	Omalizumab	IgE	off-label conflicting results not recommended [106-110]	approved	approved
	Ligelizumab	IgE	-	-	Phase III (NCT03437278) [69,70]
	Quilizumab	IgE, membrane-bound	-	-	failed primary end point [72]
	Rituximab	CD20	off-label conflicting results	-	off-label case reports [73]

			more studies needed [102-105]		
	Tralokinumab	IL-13	Phase II (NCT03526861) promising study results [115]	discontinued	-
	Lebrikizumab	IL-13	Phase II (NCT03443024) studies without TCS use needed to evaluate efficacy as monotherapy[114]	discontinued	-
	Tezepelumab	TSLP	Phase II (NCT03809663) studies without TCS use needed to evaluate efficacy as monotherapy	Phase II promising results moved to phase III (NCT03347279) [126]	-
	ANB020	IL-33	Phase II (NCT03533751)	Phase II (NCT034699934)	-
	REGN3500	IL-33	Phase II (NCT03738423)	Phase I (NCT03112577)	-
	GSK3772847	IL-33R	-	Phase II (NCT03207243)	-
	Fevipiprant	CRTh2 antagonist	Phase II (NCT017856029	Phase III (NCT03215758)	-
Others	**Nemolizumab**	IL-31a	Phase II (NCT03100344) shows efficacy on pruritus and EASI [116,117]	-	-
	Fezakinumab	IL-22	Phase II (NCT01941537) effective in a subset of patients [123]	-	-
	KHK4083 and KY1005	OX40	Phase II (NCT03703102, NCT03754309) recruiting	-	-
	AK002	Siglec8		-	Phase II (NCT03436797) active

Table 2. Textbox: Milestones achieved for asthma

A. Key publications establish asthma heterogeneity phenotypes and endotypes

i. Asthma: defining of the persistent adult phenotypes (2006) [127]

ii. Endotyping asthma: new insights into key pathogenic mechanisms in a complex, heterogeneous disease (2008) [128]

iii. Asthma endotypes: a new approach to classification of disease entities within the asthma syndrome (2011) [129]

iv. Asthma phenotypes: the evolution from clinical to molecular approaches (2012) [15]

B. Establishment of global guidelines in asthma treatment

C. Defining asthma severity

i. WHO severe asthma definition (2010) [130]

ii. ERS/ATS severe asthma definition (2014) [23]

D. Key phase III trials of biologicals in asthma

i. Omalizumab in severe allergic asthma (2001) [131]

ii. Mepolizumab in severe eosinophilic asthma (2012) [132]

iii. Reslizumab in severe eosinophilic asthma (2015) [34]

iv. Benralizumab in severe eosinophilic asthma (2016) [133]

Table 2. Textbox: Milestones achieved for CSU

A. Key publications in Urticaria pathogenesis
   i. Identification of the autoreactive nature of CSU (1986) [134]
   ii. First in vivo evidence of relevance of auto-IgE in CSU (2019) [57]

B. Establishment of guidelines for definition, classification, diagnosis and management of Urticaria, current version (2018) [53]

C. Key developments in diagnosis of atopic eczema
   i. Development of Urticaria Control Test (UCT) (2014) [135]

D. Key phase III trials of biologicals in CSU
   i. First placebo-controlled randomized trial with omalizumab in CSU (2011) [136]

Table 3. Textbox: Milestones achieved for AE

A. Key publications in atopic eczema pathogenesis
   i. Immune dysbalance towards a type 2 dominated immune reaction pattern
   ii. Mutations of Filaggrin give rise to a disrupted epithelial barrier (2006) [137]
   iii. Key role for adaptive immunity in AE (2011) [138]
   iv. Definition of disease endotypes (2019) [83]

B. Key developments in diagnosis of atopic eczema
   i. Development of diagnostic criteria (1980) (Hanifin and Raijka, UK criteria)
   ii. Development of severity scores (SCORAD and EASI)
   iii. Identification of biomarkers for diagnostics (2014) [121], correlation to severity (2017) [139], prediction of therapeutic response (2019) [123]

C. Establishment of guidelines for atopic eczema diagnosis and treatment, current version (2018) [88,94]

E. Key phase III trials of biologicals in AE
   i. Dupilumab for treatment of moderate to severe AE (2014) [111]

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