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An update on biologic-based therapy in asthma

Although it is recognized that airway inflammation is key to asthma pathogenesis, the marked heterogeneity in its clinical course and variations in response to treatment make it a challenging condition for the development of novel and effective biologic-based therapies. Biopharmaceutical approaches have identified new therapies that target key cells and mediators that drive inflammatory responses in the asthmatic lung. Such an approach resulted in the development of biologics targeted at inhibiting IL-4, IL-5 and IL-13. With the notable exception of the anti-IgE monoclonal antibody omalizumab, early clinical trials with cytokine-targeted biologics in patients with asthma were, for the most part, disappointing, despite being highly effective in animal models of asthma. It is becoming apparent that significant clinical effects with anticytokine-based therapies are more likely in carefully selected patient populations that take asthma phenotypes into account. The development of discriminatory biomarkers and genetic profiling may aid identification of such patients with asthma. This review summarizes recent evidence demonstrating the effectiveness or otherwise of monoclonal antibody-based therapies in patients with asthma.

KEYWORDS: asthma ■ biologics ■ eosinophil ■ IL-4 ■ IL-5 ■ IL-13 ■ TNF- α

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Asthma represents a complex and heterogeneous chronic disease with diverse inflammatory events that lead to structural and functional changes in the lungs, including goblet cell hyperplasia, airway smooth muscle hypertrophy and subepithelial fibrosis in the airways that in turn give rise to airway hyperresponsiveness (AHR) and reversible airflow limitation [1]. The processes that underlie asthma are characterized by different patterns of cytokine-based inflammation involving diverse cell types such as T cells, B cells, mast cells, eosinophils, basophils, neutrophils and dendritic cells, as well as structural cell types including epithelial, smooth muscle and mesenchymal cells. Accumulating knowledge has driven the development of biological therapies that target the cytokines important in asthma pathobiology [2]. For the majority of asthmatic individuals, inhaled glucocorticoids (GCs) remain the gold-standard therapy because of their potent anti-inflammatory properties that primarily reduce AHR and exacerbations, while improving lung function and quality of life [101]. However, they have well-documented side effects that may contribute to problems of compliance in some patients and are symptomatic medications that require lifetime therapy, with asthma symptoms returning if GCs are withdrawn [3]. It is now generally accepted that asthma is a complex, heterogeneous mixture of syndromes that can be subdivided into several phenotypes on

the basis of clinical, physiological and inflammatory markers [4]. Recently, our understanding of the various phenotypes of severe asthma and the identification of biomarkers for each of these phenotypes has improved. Furthermore, the concept of the endotype has been gaining acceptance with regard to the various subtypes of the disease, which are classified according to their unique functional or pathophysiological mechanisms [2,5].

Approximately 5% of patients have severe refractory asthma that responds poorly or not at all to high-dose inhaled or systemic GC treatment, and these patients account for approximately half of health spending on asthma [6]. The mechanisms underlying this inadequate control of symptoms remain poorly understood. This review, based on English-language original articles in PubMed or Medline that reported significant clinical findings published in the last 5 years, will update the current status, therapeutic potential and potential problems of targeting cytokines in asthma therapy.

IgE inhibitors

IgE is central to the pathogenesis of diseases associated with immediate hypersensitivity reactions, such as allergic asthma. IgE binds to high-affinity (Fc ϵ RI) receptors on mast cells and basophils, and to low-affinity (Fc ϵ RII) receptors on macrophages, dendritic cells and

B lymphocytes. Allergens crosslink adjacent cell surface Fab components of IgE thereby activating intracellular signal transduction. This results in mast cell release of preformed mediators and synthesis and release of other mediators that contribute to bronchoconstriction and airway inflammation.

The anti-IgE biologic omalizumab (Xolair®, Genentech/Novartis), is a US FDA/EMEA-approved humanized monoclonal antibody (mAb) to the FcεRI (Cε3)-binding domain of human IgE. Early studies demonstrated inhibition of early- and late-phase allergen-induced asthmatic reactions with serum-free IgE concentrations reduced to less than 5% of baseline [7]; omalizumab may also be able to suppress new IgE production. Furthermore, through inhibition of binding of IgE to FcεRI expressed on dendritic cells, omalizumab can reduce the efficiency of antigen presentation to T lymphocytes [8].

In clinical studies, positive outcomes were reported in a large Phase II trial that studied fortnightly intravenous (iv.) administration of omalizumab for 20 weeks in 317 patients [9] and also in two Phase III trials, including over 500 patients each, which studied subcutaneous (sc.) omalizumab every 2–4 weeks for 12 months [10,11]. In patients with moderate-to-severe allergic asthma whose symptoms were poorly controlled by high doses of inhaled GCs, 12-month administration of omalizumab resulted in a 50% reduction in their asthma deterioration-related incidents [12]. Another study reported that omalizumab treatment of subjects with both persistent rhinitis and difficult-to-treat asthma resulted in significantly reduced asthma exacerbations and improvement in the Asthma Quality of Life Questionnaire score over the 28-week study period [13]. Omalizumab has also been shown to be beneficial as an add-on therapy in severe persistent asthmatics with inadequately controlled symptoms despite best available treatment, thus reducing the occurrence of disease exacerbations, emergency hospital visits and hospitalizations [14]. A pooled analysis of six controlled clinical trials that evaluated the effect of add-on omalizumab in patients with severe persistent allergic asthma reported significant improvements in quality-of-life indices [15]. These findings support the use of omalizumab as an efficacious therapy for patients with symptomatic moderate-to-severe allergic asthma despite treatment with GCs and rescue medication. Omalizumab reduces the frequency of exacerbations and GC and β₂-agonist usage, and improves symptom control, with improved

patient quality of life and significant improvements in lung function as measured by peak expiratory flow rate and forced expiratory volume in 1 s (FEV₁). Omalizumab has a good risk–benefit profile with few side effects reported in these studies and no reports of circulating antibodies against omalizumab. However, the FDA has a black-box warning on the potential for omalizumab-induced anaphylaxis presenting as bronchospasm, hypotension, syncope, urticaria and/or angioedema of the throat or tongue. The Omalizumab Joint Task Force reported that, out of 39,510 patients receiving omalizumab, 25 had 41 episodes of anaphylaxis. The task force recommends that physicians prescribing omalizumab instigate postadministration wait periods combined with education of patients with regard to an anaphylaxis [16,17]. An analysis of omalizumab-treated patients that examined the incidence of malignancy using comprehensive pooled data from clinical trials concluded that a causal relationship between omalizumab and malignancy was unlikely [18].

Anti-IL-5

Eosinophils are not normally present in healthy lung tissue, but their accumulation is a well-defined feature of the inflammatory processes in the lungs of patients with eosinophilic asthma. In the lung, tissue eosinophils release their potent proinflammatory arsenal including granule-derived basic proteins, lipid mediators, cytokines and chemokines. These mediators potentiate airway inflammation and contribute to lung tissue remodeling, which includes airway thickening, fibrosis and angiogenesis, together with a significant contribution to asthma exacerbations [19]. Eosinophilic asthma is a phenotype of the condition characterized by increased blood or sputum eosinophils whose numbers correlate with disease severity [20]. Patients with severe disease and the refractory eosinophilic asthma phenotype often suffer frequent asthma exacerbations that may require intensive treatment with daily oral GCs in a hospital setting, with attendant side-effect and quality-of-life issues. It is well established that IL-5 plays a crucial role in the development and release of eosinophils from bone marrow, their enhanced adhesion to endothelial cells lining the postcapillary venules, and their activation, secretion and prolonged survival through apoptosis inhibition in the tissues [21,22]. IL-5 was therefore identified as a promising target to prevent or blunt eosinophil-mediated inflammation in patients with asthma and other eosinophil-related conditions,

leading to the development of humanized anti-IL-5 mAb, such as mepolizumab and reslizumab or benralizumab, a mAb against the human IL-5R α [23].

■ Mepolizumab

Early clinical trials with the anti-IL-5 biologic mepolizumab (GlaxoSmithKline) in patients with mild-to-severe asthma reported significant reductions in blood and sputum eosinophil numbers, but clinical outcomes were disappointing; for example, there was no effect on allergen-induced airway narrowing or AHR [24–26] as the majority of subjects were recruited on the basis of clinical and physiological characteristics that did not specify the presence of eosinophilic airway inflammation [27]. Furthermore, asthma management strategies aimed at the assessment of eosinophilic airway inflammation through the use of induced sputum in addition to clinical manifestations of the condition are associated with a reduction in the frequency of exacerbations [28–30]. Two proof-of-concept randomized, double-blind, placebo-controlled, parallel-group studies demonstrated that monthly infusions of mepolizumab 750 mg in patients who manifested eosinophilic asthma not only reduced eosinophil numbers in the blood and sputum, but also resulted in a significant reduction in asthma exacerbations [31,32]. These studies in highly selected asthma patient populations demonstrate that mepolizumab attenuates aspects of eosinophil-induced airway inflammation refractive to GC therapy and may therefore potentially interfere with eosinophil-induced airway remodeling in addition to reducing asthma exacerbations. Recent findings from the DREAM study are of particular interest. Pavord and colleagues report findings from a randomized placebo-controlled study of 616 patients (12–74 years) from 81 centers in 13 countries with poorly controlled asthma with evidence of eosinophilic inflammation who had two or more asthma exacerbations (the primary outcome measure) requiring treatment with oral GC in the last year [33]. Patients were treated with iv. mepolizumab (75, 250 or 750 mg) or matched placebo every 4 weeks for 12 months. Clinically significant asthma exacerbations were 2.40 per patient/year in the placebo group compared with 1.24 in the mepolizumab 75-mg group (48% reduction, 95% CI: 31–61%; $p < 0.0001$), 1.46 in the 250 mg mepolizumab group (39% reduction, 95% CI: 19–54%; $p = 0.0005$), and 1.15 in the 750 mg mepolizumab group (52% reduction, 95% CI: 36–64%; $p < 0.0001$). Thus, there was

no dose–response effect for mepolizumab in this study, nor was treatment associated with consistent improvements in symptoms or lung function. However, in the small subgroup ($n = 94$), in the study in whom sputum induction was performed, there was a dose-related fall in sputum eosinophilia with a ratio to placebo value of 0.68, 0.35 and 0.12, for mepolizumab 75, 250 and 750 mg, respectively. Moreover, the fact that the lowest dose of mepolizumab was effective is encouraging from the point of view of minimizing any potential adverse events and may inform the selection of an optimal dose for administration of mepolizumab through the sc. route. Such a marked dissociation between clinical and functional measurements and exacerbations suggests that they represent different aspects of the disease, with separate underlying pathophysiology. An interesting aspect of the DREAM study was the manner in which patients were selected for study inclusion. Rather than using a sputum eosinophilia of 3%, as in the earlier proof-of-concept studies [31,32], the DREAM investigators used less direct markers for the presence of eosinophilic airway inflammation; namely a peripheral blood eosinophil count of more than $0.3 \times 10^9/L$, increased exhaled nitric oxide greater than 50 ppb or a rapid deterioration in asthma control following a 25% or more reduction in maintenance inhaled or oral GCs. The use of an elevated blood eosinophilia is an important step forward as it simplifies the identification of asthmatic patients likely to respond to mepolizumab, rather than the use of a sputum eosinophilia, a technique only available in highly specialized centers that requires a high degree of technical and interpretative expertise.

The results of these three placebo-controlled randomized studies demonstrate that mepolizumab is efficacious in patients with specific phenotypes of severe asthma characterized by persistent, glucocorticosteroid-resistant eosinophilia; re-emphasizing the importance of the pathogenic role of the IL-5–eosinophil axis in selected subgroups of patients with severe asthma, with special regard to the recurrence of asthma exacerbations.

■ Reslizumab

Reslizumab (Cinquil™, Teva Pharmaceuticals; formerly SCH-55700) was humanized from an anti-IL-5 antibody (JES1–39D10) originally raised in rats [34]. Reslizumab was synthesized by CDR grafting of 39D10 to produce a humanized IgG4/ κ antibody with high affinity for human IL-5 with a dissociation constant of 81 pM and

an association rate constant of 4.9×10^5 per m/s. Proliferation of human erythroleukemia cells induced by IL-5 was inhibited by reslizumab with an EC_{50} value of 45 pM. Reslizumab was evaluated in allergic mice and *Ascaris*-responsive monkeys, in which eosinophilic inflammation was inhibited by a single dose of reslizumab (1 mg/kg intraperitoneally) that exhibited a long duration of action [35,36].

An early clinical trial in patients with severe asthma whose symptoms were not controlled by inhaled corticosteroids demonstrated that, although there was a profound reduction in circulating eosinophils, treatment with reslizumab did not result in significant improvements in asthma symptoms or lung function. Reslizumab exhibited a terminal half-life of approximately 25 days in asthmatic patients with doses of 0.3 mg/kg. Maximal effect on decreases in peripheral blood eosinophilia was observed at a dose of 1.0 mg/kg, which was sustained for at least 4 weeks after administration, with a return to baseline values observed at 5–6 months postdosing [37]. A recent Phase II, randomized, placebo-controlled, multicenter trial evaluated iv. reslizumab in asthmatic patients with symptoms not controlled by high-dose inhaled GC and who had a sputum eosinophilia >3%. Compared with placebo (n = 53), the reslizumab group (n = 53; 3.0 mg/kg) exhibited a modest (reslizumab: -0.7; placebo: -0.3) but nonsignificant (p = 0.054) improvement in asthma control as assessed by the Asthma Control Questionnaire score (the primary study end point) in the population as a whole. In patients with concomitant nasal polyposis, a hallmark of eosinophilic disease in patients with asthma [38], reslizumab treatment was associated with a significant improvement in asthma symptoms (reslizumab: -1.0; placebo: -0.1; p = 0.012). Reslizumab significantly decreased sputum eosinophilia together with modest but significant (p = 0.002) mean changes from baseline to end of therapy in FEV₁ of 0.18 and -0.08 l for the reslizumab and placebo group, respectively, after 15 weeks. There was a nonsignificant reduction in asthma exacerbations in the reslizumab group while the improvement noted in pulmonary function did not differ between those patients with and without nasal polyps. Adverse events for reslizumab included nasopharyngitis, fatigue and pharyngolaryngeal pain but these were similar to placebo without evidence of rebound eosinophilia [39]. These findings have led to the instigation of several asthma Phase III clinical trials of reslizumab and these are currently

underway [40]. Reslizumab may also prove efficacious in other inflammatory diseases with a marked eosinophilic component [41].

■ Benralizumab

Benralizumab is a novel humanized afucosylated IgG1κ mAb indicated for the potential treatment of asthma and chronic obstructive pulmonary disease that binds to a distinct epitope within the extracellular domain of recombinant human IL-5Rα. At the time of publication, benralizumab was undergoing Phase II clinical trials in both the specified indications [102,103]. Afucosylation is associated with enhanced antibody-dependent cell cytotoxicity, and benralizumab was found to induce apoptosis in eosinophils and basophils [42]. Other anti-IL-5 mAbs act by neutralizing the effects of IL-5, whereas benralizumab targets the effector cells, mainly eosinophils and basophils, many of whose functions are driven by IL-5. Tissue eosinophils resident in bronchial biopsies of patients with mild atopic asthma exhibited intense immune positivity for benralizumab in contrast with resident mast cells, which were negative [29]. These findings indicate that benralizumab binds human lung tissue-resident eosinophils expressing IL-5Rα and could delete these cells through induction of apoptosis, thereby acting as a potential asthma therapeutic [43]. Indeed, a Phase I study in subjects with mild asthma demonstrated that iv. benralizumab (0.3–3.0 mg/kg) rapidly induced near total depletion of peripheral blood eosinophils while exhibiting an adequate safety profile and dose-proportional pharmacokinetics [44].

IL-4 & IL-13

Eosinophil involvement as a major proinflammatory effector cell in asthma is well established [45] with Th2 cells that express IL-4, IL-5 and IL-13 representing essential and central coordinators of asthmatic inflammation [46]. Both IL-4 and IL-13 are important in eosinophil accumulation and are key factors in IgE synthesis by B cells [47]. There is also evidence that, in asthma, IL-13 may act directly on airway smooth muscle cell contractility [48–50]; this, together with direct effects of IL-13 on epithelial cells and mucus production [51], may contribute to AHR and airway narrowing. The genes encoding IL-4 and IL-13 are located on the cytokine cluster on chromosome 5q31; both cytokines share some structural similarities. Each exerts their actions through the IL-4Rα/IL-13Rα1 receptor complex, which then activates the transcription factor STAT-6 [52]. They therefore have multiple overlapping

functions, although IL-4 has independent effects via the IL-4R α / γ receptor.

Receptors for IL-13 are expressed by a multitude of cell types important in the pathogenesis of asthma including eosinophils, mast cells together with structural airway epithelial cells, fibroblasts and smooth muscle cells. In asthma, the most important cellular sources of IL-13 are T cells, mast cells and eosinophils. Increased levels of IL-13 have been reported in the sputum and bronchial biopsies from patients with asthma, which correlated with increased eosinophil numbers [53,54]. Importantly, mast cells expressing IL-13 are present within the airway smooth muscle in asthmatic subjects suggesting a pivotal role for IL-13 in interactions between these cell types [55]. IL-13 may also have direct effects on airway smooth muscle function by enhancing the contraction effect of acetylcholine [56]. It is now widely appreciated that the asthmatic airway epithelium is intrinsically abnormal and critically contributes to the airway inflammatory response [57]. An important aspect of IL-13 therefore is the effect it has on the functions of airway epithelial cells including induction of a hypersecretory state [58] and reduced barrier function through downregulation of proteins associated with maintaining epithelial tight junctions [59]. IL-13 is a potent promoter of epithelial cell TGF- β production, which in turn activates myofibroblasts and is also involved in extracellular matrix deposition leading to sub-epithelial membrane thickening, both thought to contribute to airway remodeling [60,61]. IL-13 therefore appears to represent a potentially effective target for asthma therapy [62].

■ Lebrikizumab

A randomized, multicenter study of the anti-IL-13 biologic lebrikizumab (Genentech/Chugai Pharmaceutical) has recently demonstrated that it significantly improved lung function in patients with inadequately controlled asthma, but only in a subgroup defined on the basis of high serum levels of periostin [63]. The latter is a cellular matrix protein that is released by airway epithelial cells stimulated with IL-13. Periostin exhibits effects on epithelial cells and fibroblasts that may contribute to airway remodeling in asthma [64,65]. Indeed, at week 12, the reported FEV₁ increase was 5.5% in the whole lebrikizumab-treated group, 8.2% in the high-periostin subgroup and 1.6% (not significant) in the low-periostin subgroup, compared with baseline values. Exhaled nitric oxide also serves

as a proinflammatory, if less specific, marker in asthma. Interestingly therefore, a *post hoc* analysis revealed that lebrikizumab-treated patients with nitric oxide values above the group median exhibited larger improvements in FEV₁ than those patients with lower levels. In terms of safety, frequency of adverse events were similar in the two groups (74.5% in the lebrikizumab group and 78.6% in the placebo group), as was the frequency of severe adverse events (3.8 and 5.4% in the two groups, respectively).

■ Tralokinumab

Tralokinumab (CAT-354, MedImmune), is an injectable anti-IL-13 humanized IgG4 mAb for the potential treatment of asthma. Tralokinumab potently neutralizes IL-13 and has been shown to inhibit a range of IL-13-mediated effects in preclinical studies; Phase I studies have demonstrated linear pharmacokinetics and an acceptable safety profile over the dose range tested [66,67]. A recent proof-of-concept study evaluated the effect of sc. tralokinumab (150, 300 or 600 mg) or placebo in 194 adults with moderate-to-severe uncontrolled asthma who maintained their existing controller therapy [68]. Compared with placebo there were improvements in lung function (FEV₁) with a dose-response evident at the same time point with mean $\pm$ SD increases from baseline in FEV₁ of 0.16 $\pm$ 0.35 l (p = 0.299), 0.21 $\pm$ 0.37 l (p = 0.102) and 0.26 $\pm$ 0.41 l (p = 0.041) in the 150, 300 and 600 mg tralokinumab treatment groups, respectively. There was also a reduction in the use of short-acting β 2-agonists with no significant improvement in Asthma Questionnaire (ACQ)-6 score. Furthermore, when a subgroup of patients were stratified into sputum IL-13-positive or -negative (<10 pg/ml¹) there were no differences in the response to tralokinumab. All adverse events were mild to moderate and were not determined to be related to treatment with tralokinumab. These findings support those with lebrikizumab (see above) in that both studies report some improvement in lung function following anti-IL-13 therapy. Larger trials will be required to confirm these initial findings and also to assess what effects these drugs may have upon asthma exacerbations and patient-reported outcomes.

■ Pitrakinra

A recombinant human IL-4 variant, pitrakinra (AerovantTM, Aerovance), was developed that competitively inhibits the IL-4R α receptor complex to interfere with the actions of both

IL-4 and IL-13 and initial clinical trials indicated that such an approach may prove beneficial in patients with atopic asthma (reviewed in [69]). A more recent double-blind, randomized, placebo-controlled trial of inhaled pitrakinra in 534 patients with uncontrolled, moderate-to-severe asthma reported significant effects on exacerbations rates and symptom scores in patients with an elevated blood eosinophilia [70]. However, another recent 12-week clinical trial with a mAb directed at the IL-4R α (AMG-317, Amgen) reported significant reductions in blood IgE levels and eosinophils, but found no significant change in measured asthma outcomes [71]. It is interesting to note that analysis of single nucleotide polymorphisms leading to amino acid changes in the 3' end of the IL-4R α gene identified a subgroup of patients with moderate-to-severe asthma who were significantly more responsive to pitrakinra therapy.

■ Dupilumab

Dupilumab (SAR231893/REGN668), is a fully humanized mAb to the IL-4R α /IL-13R α 1 receptor complex that inhibits both IL-4 and IL-13 signaling. A multicenter randomized, double-blind, placebo-controlled, parallel-group Phase IIa study evaluated dupilumab in patients with moderate-to-severe asthma, with a blood eosinophil count of ≥ 300 cells/ μ l or a sputum eosinophil level greater than 3% who used medium-to-high dose inhaled GCs plus long-acting β -agonist. Dupilumab (300 mg; 52 patients) or placebo (52 patients) was administered sc. for 12 weeks. The primary outcome measure was frequency of disease exacerbations with a range of measures of asthma control as secondary outcomes. Asthma exacerbations occurred in 26 patients: three receiving dupilumab (6%) and 23 receiving placebo (44%) (odds ratio with dupilumab: 0.08; 95% CI: 0.02–0.28; $p < 0.001$); giving an 87% relative reduction in the proportion of patients experiencing medication withdrawal-induced exacerbation in the 12-week study period. At week 2, dupilumab treatment was also associated with a significant increase from baseline in both predicted and actual FEV₁ that was maintained through to week 12 despite the instruction to subjects to discontinue their long-acting β -agonist therapy at week 4 and to taper and stop inhaled GCs during weeks 6–9 [72]. These are very encouraging findings that support a significant pathogenic role for both IL-4 and IL-13 in persistent, moderate-to-severe eosinophilic

asthma, and that targeting both of these cytokines is more effective than inhibiting either alone. In contrast, the studies of lebrikizumab and tralokinumab reported improvements in lung function but not in asthma symptoms, reduced β -agonist use or improved quality of life. Moreover, although treatment with anti-IL-5 mAb reduced rates of asthma exacerbation, there were no significant improvements in lung function or symptoms. Dupilumab also significantly reduced serum IgE, eotaxin-3, TARC and exhaled nitric oxide, all of which associated with Th2-driven inflammation. In terms of adverse events, injection-site reactions, nasopharyngitis, nausea and headache occurred more frequently with dupilumab than placebo. The authors acknowledged that the short study period and the way in which exacerbations were defined may not represent 'real-world' asthma and that further studies are required to confirm and extend their findings [73]. Dual inhibition of IL-4 and IL-13 represents a very promising avenue for biologic-based asthma therapy, but further large-scale clinical trials on patients with day-to-day asthma are required to fully validate such an approach.

■ TNF- α

TNF- α is an innate immune response cytokine that has been implicated in chronic inflammatory conditions that include rheumatoid arthritis and Crohn's disease with anti-TNF- α therapy proving to confer beneficial effects. Macrophages are a major source of TNF- α with significant contributions from other pro-inflammatory cells including monocytes, dendritic cells, B lymphocytes, T cells, neutrophils, mast cells and eosinophils, together with the structural cells fibroblasts, epithelial cells and smooth muscle cells. TNF- α has proinflammatory effects on eosinophils, neutrophils, T cells, epithelial cells and endothelial cells. It may also have a key role in amplifying airway inflammation through activation of transcription factors such as NF- κ B and AP-1. Studies of biopsies and lavage fluid from the airways of patients with severe asthma have shown elevated TNF- α levels compared with samples from subjects with well-controlled disease. TNF- α may contribute to AHR, airway remodeling and GC resistance in asthma, thereby representing a potential target for therapy. Humanized murine anti-TNF mAb (infliximab) and a soluble TNF receptor linked to human IgG1 (etanercept) have been developed and have been evaluated for asthma treatment [74].

The ACQ score, FEV₁, PEF and bronchial hyperresponsiveness to methacholine in patients with severe asthma were significantly improved by sc. etanercept (25 mg twice weekly for 12 weeks) [75], while significant outcomes on symptoms and lung function were reported in patients with severe refractory disease [76]. In contrast, a larger placebo-controlled randomized trial in patients with moderate-to-severe persistent asthma reported no significant differences in respiratory function, airway hyperresponsiveness, quality of life and exacerbation rate following sc. etanercept 25 mg given twice weekly for 12 weeks [77]. A more recent clinical trial with the anti-TNF biologic golimumab in patients with severe uncontrolled persistent asthma reported negative clinical findings. However, a subgroup analysis of the patients demonstrated that the drug was beneficial in older patients with late-onset asthma, a history of hospitalizations or emergency visits during the year before screening and who also had lower baseline FEV₁ levels with a postbronchodilator FEV₁ increase of more than 12%. Importantly, this study was terminated early due to unacceptable adverse events, including frequent serious infections, eight malignancies and one death in the active-treatment group compared with the placebo group [78]. Overall it appears that identification of the correct patient population may improve clinical outcomes for TNF- α inhibitors [79], but the unfavorable risk–benefit ratio exhibited by golimumab does cast doubt on the future of anti-TNF therapy in severe asthma.

Conclusion & future perspective

Inhaled GCs remain the gold standard treatment for asthma because they suppress multiple inflammatory mechanisms in parallel. However, those patients with GC-refractory eosinophilic asthma represent a clear and pressing unmet medical need. Until relatively recently the development of novel asthma anti-inflammatory therapy based on targeting cytokines has proven to be, for the most

part, disappointing. The majority of biologics have proven inadequate in the clinical setting in asthma, even though they were highly effective in animal models of asthma. The development of discriminatory biomarkers and genetic profiling may identify patients with particular subphenotypes of asthma, a point illustrated by the recent studies that suggest that mepolizumab therapy has beneficial effects in carefully selected patient populations. However, issues remain with regard to the cost of biologics, determination of the most effective biomarkers to select responsive patients and whether treatment with biologics should be confined to specialist asthma centers [80]. One other important consideration is that the placebo group in trials of biologics in asthma often exhibit a marked improvement in symptoms, which may reduce the likelihood of significant findings being observed for the test compound. This phenomenon has several potential explanations including suggestibility, natural disease variability and improved compliance with concomitant anti-inflammatory therapy or regression to the mean [81]. Perhaps the most important recent development is the evidence provided by the pitakinra and dupilumab studies; these strongly suggest the effectiveness of novel biologics that are targeted at more than one cytokine and/or chemokine. In terms of safety, one major issue is that of the potential or actual side effects of novel compounds that are designed to interfere with important aspects of both the innate and acquired immune systems as exemplified by the unacceptable adverse effects associated with golimumab treatment in patients with severe uncontrolled asthma. Recent rapid advances in our understanding of the role that the innate immune response plays in asthma also provided potential therapeutic targets beyond the Th2 pathway [82]; for example, TSLP, IL-25 and IL-33 are a triad of cytokines released by airway epithelial cells in response to various environmental stimuli or by cellular damage. They act in concert to drive Th2 polarization through overlapping mechanisms, causing remodeling

Executive summary

- Omalizumab reduces exacerbations, improves symptom control, reduces glucocorticoid and β_2 -agonist usage, improves patient quality of life, together with significant improvements in lung function and has a favorable risk–benefit profile.
- Mepolizumab is efficacious in patients with specific phenotypes of severe asthma characterized by persistent, glucocorticosteroid-resistant eosinophilia.
- Reslizumab may also prove to be efficacious in patients with a similar asthma phenotype.
- Dual inhibition of IL-4 and IL-13 with dupilumab represents a very promising avenue for biologic-based asthma therapy, but further large-scale clinical trials on patients with day-to-day asthma are required to fully validate such an approach.

and pathological changes in the airway walls, suggesting pivotal roles in the pathophysiology of asthma [83]. They therefore represent potential development targets for novel biologics. In conclusion, it is hoped that a combination of targeting therapy to carefully selected asthmatic patient populations, together with the development of biologics that target more than one cytokine may lead to significant advances in this area over the next 5 years.

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GM Walsh has no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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