



The emergence of new biologics for severe asthma

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Patients with severe asthma experience severe symptoms and frequent exacerbations despite intensive treatment with inhaled and oral glucocorticoids. Biologics for severe asthma aim to reduce asthma-related and glucocorticoid-induced morbidity. Recently, new biologics targeting interleukin (IL)-5, IL-5 receptor and IL-4/IL-13, which are all cytokines involved in so-called type 2 airway inflammation, were approved for severe asthma. They show a reduction in exacerbation rate and an oral glucocorticoid-sparing effect. Studies with upstream biologics targeting alarmin cytokines such as thymic stromal lymphopoietin (TSLP) and IL-33 are underway, and newly designed bispecific antibodies targeting more than one pathway are in early phases of development. Such pathway-targeted add-on treatments will soon become standard of care for all patients with severe asthma.

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Introduction

Severe asthma is a debilitating disease, associated with frequent severe exacerbations and poor quality of life [1^{••}]. Until recently, patients with this condition were dependent on the chronic use of high dose inhaled and oral glucocorticoids. Long-term maintenance therapy with oral glucocorticoids can increase the risk of serious and life-threatening adverse events [2,3]. Moreover, recurrent short courses of glucocorticoids for treatment of exacerbations as well as high doses of inhaled corticosteroids contribute to the systemic adverse effects of glucocorticoid therapy [3,4]. Fortunately, the recent introduction of biologics for severe asthma has led to improvements with respect to treatment diversity for

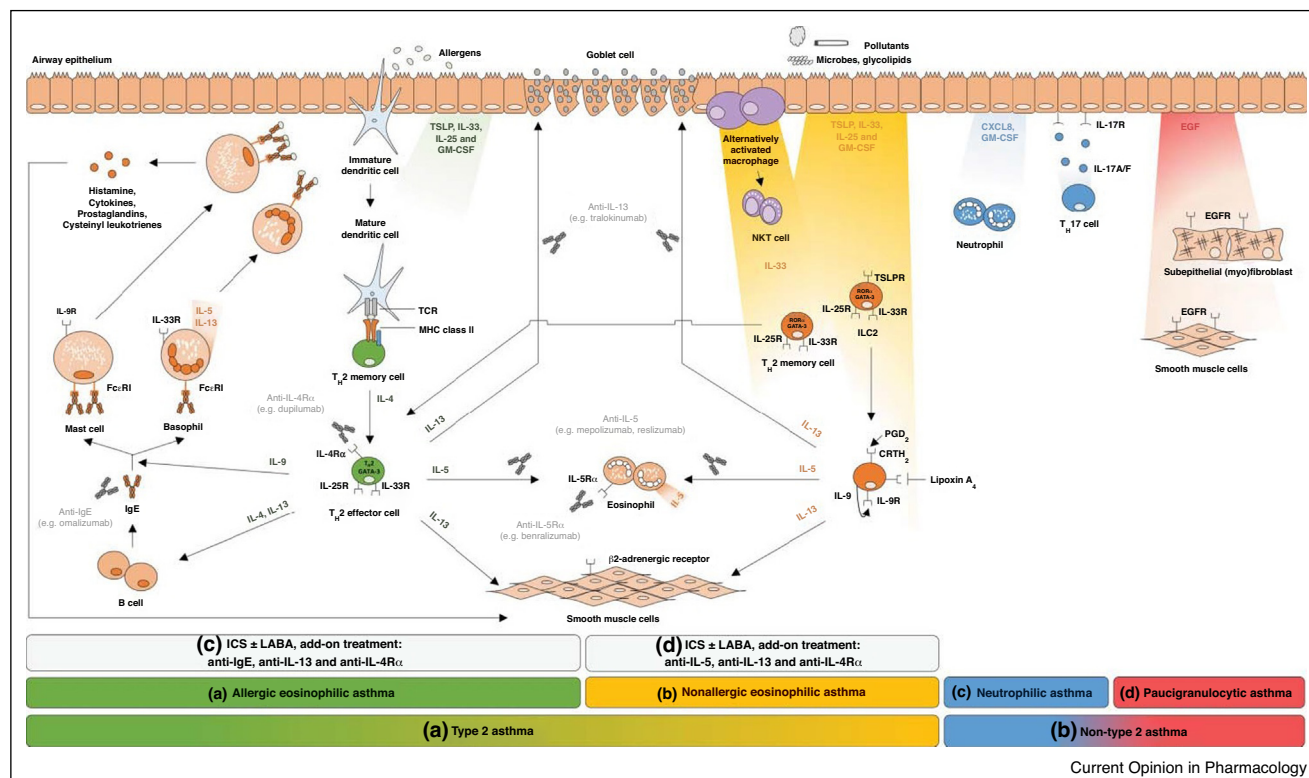
patients with severe asthma. In 2003, omalizumab, a monoclonal antibody that binds Immunoglobulin (Ig)E, was the first FDA approved biologic for treatment of severe allergic asthma [5]. More than a decade later the development of biologics came in a fast track. Several biologics targeting key cytokines of so-called type 2 airway inflammation (interleukin (IL)-4, IL-5, IL-13) [6] were tested in phase 3 studies and 4 of these are now FDA approved. These include therapies targeting IL-5 (mepolizumab [7–9], reslizumab [10–12]), the IL-5 receptor (benralizumab [13,14,15^{••}]) and the alpha subunit of the IL-4 receptor (IL-4Rα, dupilumab [16^{••},17^{••}]), and have resulted in impressive reductions in asthma morbidity. Other biologics, unfortunately, failed in phase 2 (anti-IL-4R [18]) and phase 3 studies (anti-IL-13 [19[•],20[•]]). Promising upcoming treatments interfering with more upstream molecules, such as alarmins, transcription factors and receptors expressed on immune cells, are entering phase 3 trials [21^{••},22,23].

So fortunately, there is a growing number of treatment options for patients with severe asthma who remain uncontrolled despite high dose inhaled or oral glucocorticoids and experience recurrent exacerbations. This review will give an update on the most recent developments in the fast moving field of biologic treatment for severe asthma.

Current concepts on asthma pathophysiology

Asthma is a heterogeneous, inflammatory airway disorder with complex pathophysiologic mechanisms [24]. Knowledge on the different asthma phenotypes and their differential pathophysiology is exponentially increasing. However, exact mechanisms and pathways of asthma pathogenesis are not yet clear. In 1940, Rackemann suggested that eosinophils played an important role in ‘extrinsic’ or allergic and ‘intrinsic’ or non-allergic asthma [25]. In the following decades, the focus moved toward airway smooth muscle spasm and airway hyperresponsiveness as the most important underlying mechanisms, but in the 90s, eosinophils were again considered key cells in all patients with asthma [26]. Initially, asthma associated with eosinophilic airway inflammation was known as Th2-high asthma because of the orchestrating role of T-helper (Th)2 cells and its cytokines (Figure 1) [27], with IL-4 driving the production of immunoglobulin E (IgE) by B-cells, IL-5 recruiting and activating eosinophils and IL-13 stimulating airway smooth muscle and mucus glands [1^{••}]. In 2011, another key immune cell was identified, the type 2 innate lymphoid cell (ILC2) [28], which is capable of releasing large amounts of IL-5 and IL-13 after exposure of the epithelium to non-specific stimuli such as microbes and pollutants [29]. Since then, ‘Th2 asthma’ was renamed as

Figure 1



Currently known pathways of airway inflammation in asthma.

Simplified schematic representation of four different types of airway inflammation in asthmatic patients: allergic eosinophilic asthma, non-allergic eosinophilic asthma, neutrophilic asthma and paucigranulocytic asthma. From Godar *et al.* [29].

‘type 2 asthma’. The mechanism of non-type 2 asthma is much less understood, although IL-17-induced neutrophilic inflammation might play an important role [30].

Interestingly, the variable effects of biologic therapy in patients with type 2 asthma provide additional insight into pathophysiologic mechanisms. Some patients are good responders to one biologic, but not to another, while others have less exacerbations but show no improvements in lung function [7,8,10,15^{**},16^{**},17^{**},31]. In addition, several pathways may be activated within the same patient, dominant pathways may change over time, depending for instance on therapy or triggers, or the blockage of one pathway could stimulate another [32–35]. This illustrates that the network of inflammatory pathways in asthma is complex and dynamic, and interacts with environmental factors. Given this complexity, there is an urgent need to identify pathway-related biomarkers to target the right pathways in each individual patient.

Currently approved and failed biologics targeting type 2 inflammation

Fifteen years after omalizumab became available for patients with severe allergic asthma in 2003, biologics

targeting the eosinophil were introduced, including antibodies against IL-5 or IL-5 receptor [7,8,10,11,13,14]. Mepolizumab, reslizumab and benralizumab were approved by the FDA in 2015, 2016 and 2017, respectively, for severe eosinophilic asthma in adults and children ≥ 12 years (except for reslizumab that was approved for adults only and mepolizumab that was approved by the EMA for children ≥ 6 years) [36]. They all showed a significant reduction in exacerbation rates in phase 3 studies [7,9–14]. More importantly, mepolizumab and benralizumab showed an impressive oral glucocorticoid-sparing effect [8,15**]. Post hoc analyses of phase 2 and 3 studies with these biologics showed that patients with late-onset asthma (>40 years), frequent exacerbations, impaired lung function, or chronic rhinosinusitis with nasal polypsis benefited most from anti-IL-5 treatment with greater reductions in exacerbation rates and larger improvements in forced expiratory volume in 1 s (FEV1) compared to placebo [31,37,38]. These clinical characteristics are now considered typical of the severe eosinophilic asthma phenotype [39]. Currently, there are no head-to-head studies comparing the efficacy of the 3 anti-IL-5 biologics yet, but one trial comparing omalizumab with mepolizumab in severe combined

allergic and eosinophilic asthma is underway (PREDICTUMAB) [40]. Nonetheless, there are some differences between these biologics which may be relevant to clinicians. For example, mepolizumab showed efficacy in patients with severe asthma and blood eosinophils >150 cells/L, whereas this was >400 cells/L for reslizumab and >300 cells/L for benralizumab; mepolizumab and benralizumab are given subcutaneously, whereas reslizumab is only approved for intravenous use; the approved doses of mepolizumab and benralizumab for severe asthma are fixed, whereas the dose of reslizumab is weight-adjusted; and importantly, the dosing interval of benralizumab is 8 weeks, whereas both mepolizumab and reslizumab are to be given every 4 weeks. These practical issues may be quite important for patients and physicians when choosing between different anti-IL-5 treatments (Table 1).

In addition to the anti-IL-5 therapies, another interesting biologic has become available, namely dupilumab, which targets IL-4 and IL-13 by blocking the shared IL-4R α . Two phase 3 trials investigating the effect of dupilumab in patients with moderate-to-severe asthma showed significant reductions in exacerbation rates and oral glucocorticoid-sparing effects [16^{••},17^{••}]. Dupilumab appeared to be ineffective in patients with non-eosinophilic asthma (blood eosinophil counts <150 cells/ μ L) and was therefore FDA approved in October 2018 for moderate-to-severe asthma patients aged 12 years and older with the eosinophilic phenotype or with oral glucocorticoid-dependent asthma.

As a consequence of its mode of action, dupilumab differs from the anti-IL-5 biologics in several aspects. First, in contrast to the anti-IL-5's, dupilumab does not decrease blood eosinophils [7,9,10,12–14,16^{••}]. Instead, it lowers levels of IgE and exhaled nitric oxide (FeNO), which is not the case with anti-IL-5 treatment [41]. Dupilumab has to be administered subcutaneously every two weeks, which is more frequent compared to anti-IL-5 biologics. Finally, dupilumab appears to be very effective against atopic co-morbidities like atopic dermatitis and nasal polyposis [42,43], which suggests that dupilumab could be particularly beneficial for atopic patients with combined eosinophilic asthma, dermatitis and nasal polyposis.

Unfortunately, two initially promising biologics failed to reach the market. In phase 2 studies, tralokinumab and lebrikizumab, both neutralizing antibodies against IL-13, showed positive effects on FEV1 and exacerbation rates in subgroups of patients with increased type 2 biomarkers, in particular periostin [44,45]. However, in phase 3 studies, these effects could not be reproduced [19[•],20[•]]. In line with these results, tralokinumab failed to decrease airway eosinophils in a phase 2 trial and showed no oral glucocorticoid-sparing effect in another phase 3 trial [46,47]. These failures could be

possibly a result of solely inhibiting IL-13, which may not be sufficient to reduce eosinophilic airway inflammation or to prevent exacerbations in patients with severe asthma. Further development of these anti-IL-13 antibodies for asthma has been discontinued.

Promising new developments

The next generation of biologics targeting upstream cytokines may be very promising as they interfere early in the type 2 inflammatory cascade [48]. Tezepelumab is a human monoclonal antibody against TSLP, an 'alarmin' cytokine produced by the bronchial epithelium in response to several inflammatory triggers that activates both innate and adaptive immune cells [48]. In a large phase 2 trial, tezepelumab reduced annualized asthma exacerbation rates in both patients with low and high Th2 inflammatory status (based on total IgE level and blood eosinophil count) and, in accordance to the upstream mode of action, it reduced both blood eosinophils, FeNO and total IgE serum levels [21^{••}]. Two phase 3 trials with tezepelumab are currently recruiting patients and results are eagerly awaited. IL-33 and IL-25 are two other alarmins. IL-33 is currently being investigated as potential drug target in phase 2 studies, while there are no ongoing clinical trials with anti-IL-25 [49]. Theoretically, the downside effect of upstream biologics could be immune dysregulation or suppression of host defense [50]. Therefore, patients treated with these biologics should be closely monitored. However, current evidence suggests that these drugs are safe.

Bispecific antibodies, which are in early phases of development, are another interesting class of biologics for the treatment of severe asthma. These molecules recognize two different epitopes [51] and can thereby tackle different pathways simultaneously. A neutralizing antibody targeting IL-4R α /IL-5 has been recently investigated in preclinical studies [52]. Another antibody against IL-13/TSLP has just been developed [53]. An anti-IL-13/IL-17 antibody, which might be a potential treatment option for patients with combined eosinophilic and neutrophilic inflammation (mixed granulocytic asthma [54]) or in patients with counter-regulated non-type 2 inflammation after targeted treatment of type 2 inflammation [33], has recently been tested in a phase 1 trial [55]. Further developments on bispecific antibodies will likely occur in the near future. As with upstream biologics, safety profiles should also be closely monitored with bispecific antibodies.

Two other classes of drugs, which are formally not considered to be biologics (i.e. drugs produced by living cells [29]), also have promising potential as treatment strategies for asthma. One strategy involves the modulation of receptors of key inflammatory cells [56]. Fevipiprant is an example of a small molecule inhibiting the prostaglandin D2 receptor, also known as the chemoattractant receptor-homologous molecule expressed on Th2 cells (CRTH2)

Table 1**Features of the currently FDA approved biologics**

Biologic	Target	FDA approved (yr)	Patient population with clinical benefit in phase 3 studies	Route of administration	Dosing	Interval of administration	Main effect on asthma	Effect on biomarkers
Omalizumab (Xolair)	IgE	2003	Uncontrolled moderate-to-severe allergic asthma with total IgE serum level ≥ 30 IU/mL and specific IgE or positive skin prick test to a perennial allergen and FEV $\leq 80\%$ [5,69,70]	Subcutaneous	75–600 mg, depending on weight and baseline total IgE level	2–4 weeks, depending on weight and baseline total IgE level	Reduction exacerbation rate [5,69]	-Minimal reduction in FeNO [70] -Reduction in free circulating IgE [5]
Mepolizumab (Nucala)	IL-5	2015	Severe eosinophilic asthma with blood eosinophils ≥ 150 –300 cell/ μ L, and ≥ 2 exacerbations previous year or dependent on oral glucocorticoids [7–9]	Subcutaneous	100 mg	4 weeks	-Reduction exacerbation rate [7–9] -Glucocorticoid-sparing effect [8]	Reduction blood and sputum eosinophils [7,9,41]
Reslizumab (Cinqaero)	IL-5	2016	Uncontrolled (ACQ ≥ 1.5) severe eosinophilic asthma with blood eosinophils ≥ 400 cell/ μ L [10–12]	Intravenous	3 mg/kg	4 weeks	Reduction exacerbation rate [10–12]	Reduction blood and sputum eosinophils [10–12,71]
Benralizumab (Fasenra)	IL-5R α	2017	Severe eosinophilic asthma with blood eosinophils ≥ 300 cell/ μ L, and ≥ 2 exacerbations previous year or dependent on oral glucocorticoids [13,14,15**]	Subcutaneous	30 mg	First three doses interval of 4 weeks, thereafter 8 weeks	-Reduction exacerbation rate [13,14,15**] -Glucocorticoid-sparing effect [15**]	Reduction blood and sputum eosinophils [13,14,72]
Dupilumab (Dupixent)	IL-4R α	2018	Severe eosinophilic asthma, FEV1 $\leq 80\%$, and with either blood eosinophils > 150 cell/ μ L and episode of worsening asthma previous year, or glucocorticoid dependent asthma [16**,17**]	Subcutaneous	300 mg	2 weeks	-Reduction exacerbation rate [16**,17**] -Increase FEV [16**] -Glucocorticoid-sparing effect [17**]	-Reduction FeNO and total IgE level [16**,17**] -Transient increase blood eosinophils [16**,17**]

[56,57]. Orally administered fevipiprant, showed efficacy in phase 2 trials by improving lung function in asthma patients with moderate or severe airflow limitation [58,59], and in asthma patients with sputum eosinophilia [23]. Another new treatment strategy involves the inhibition of transcription factors by catalytically active antisense oligonucleotides. SB010, an inhaled DNzyme, targets GATA-3, a key transcription factor in the type 2 inflammatory pathway [60]. This DNzyme showed effective inhibition of the early and late asthmatic response to inhaled allergens in patients with mild asthma, which was associated with a decrease in type 2 inflammatory markers [22].

Biologics for non-type 2 inflammation

No effective biologics for non-type 2 related asthma are available yet. The group of patients with non-type 2 inflammation is heterogeneous [61], which makes this group challenging to investigate [29]. Targeting neutrophilic inflammation with biologics such as anti-CXCR2, anti-TNF- α , and anti-IL-17RA failed to show efficacy in patients with asthma [62–65]. However, one trial with an anti-IL-17 antibody in patients with low type 2 status is ongoing with other biomarker targets under investigation [66]. Although there is a growing attention for non-type 2 asthma, there is currently a notable unmet need for effective therapy for these patients.

Remaining issues

With the emergence of biologic therapies for severe asthma, a significant number of patients can now be treated with a remarkable positive impact on their lives. However, there are still many unresolved issues. For instance, there are currently no adequate biomarkers to assess the dominant inflammatory pathway in an individual patient. As a consequence, biologic treatment is now given on a trial-and-error base. In addition, there is no clear definition of response to biologic therapy in patients with severe asthma nor is there consensus on the timing for evaluation of this response. Furthermore, it could be questioned whether a fixed dose of biologic therapy is suitable for all patients. Those with very severe inflammation might be under-treated, whereas others may be over-treated. Finally, it is currently not known how to manage patients who do not respond, or only partially respond to anti-IL-5 (receptor) or anti-IL-4/IL-13 biologics, who may also have residual inflammation through other non-targeted pathways [6]. Thus, many questions about biologic therapy for severe asthma remain unanswered.

Summary

Important clinical studies with biologics targeting key cytokines of the type 2 inflammatory pathways have been conducted over the last few years. These studies showed significant decreases in exacerbation rates and reductions in chronic oral glucocorticoids use, which

resulted in the approval of anti-IL-5 (receptor) and anti-IL-4/IL-13 biologics. In the next few years, research will be focused on drugs interfering with upstream targets (e.g. TSLP, IL-33, GATA-3) or drugs that simultaneously inhibit different key inflammatory cells (e.g. CRTH2 antagonists). Now that it is increasingly recognized that different pathways can be (reciprocally) activated in one single patient [6,67], future research directions may focus on combined therapies [29] or biologic therapy with bispecific antibodies. Inactivating different pathways simultaneously seems like an important research avenue, but safety will need to be carefully considered. Thus, we are getting increasingly closer to the ultimate treatment for patients with severe asthma, which is to identify accurate biomarkers of activated type 2 or non-type 2 pathways in an individual patient, and to optimize and develop (combination of) treatments that adequately target all these different activated pathways in a single patient. That would represent real precision medicine! [68].

Conflict of interest statement

Katrien Eger: nothing declared.

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