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Novel monoclonal treatments in severe asthma

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ABSTRACT

Aim: To provide a general overview of the current biological treatments and discuss their potential anti-asthmatic effects. **Data sources:** We reviewed articles in PubMed found using the search words "Asthma/therapy AND antibodies, monoclonal/therapeutic use AND cytokines." **Study selections:** Only articles published in English since 2000 were considered. The search identified 29 studies; 8 additional studies were found by hand search, generating 37 studies. **Results:** Of the 37 studies investigating biological treatments of asthma, 5 were on the effects of anti-IgE (omalizumab); 12 on anti-IL-5; 8 on anti-IL-13; 5 on anti-IL-4R- α ; 3 on anti-IL-9; one on TNF- α ; one on anti-IL-2R- α ; one on TSLP (Thymic Stromal Lymphopoietin); and one on OX40L. Sample sizes ranged from 3 to 943 participants. Studies of therapies targeting IgE, IL-2, IL4R- α , IL-5, and IL-13 showed some efficacy, whereas those targeting TSLP, IL-9, and TNF- α lacked convincing effectiveness. **Conclusion:** Research on the biological treatment of asthma shows promising results. While anti-IgE (omalizumab) has been used in the treatment of asthma for some years, anti-IL-5 has recently been approved for use. The efficacy of results of other large studies with a longer duration is needed to draw a firm conclusion. Such studies should not only focus on clinical outcomes, but also consider asthma-related quality of life. Knowledge on the asthma phenotypes and identification of biomarkers associated with these will be useful for physicians considering the right treatment for the asthma patient.

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Introduction

Asthma is a chronic inflammatory disorder of the airways associated with airway hyperresponsiveness, variable airflow obstruction, and airway inflammation. Clinically, asthma is characterized by recurrent episodes of coughing, wheezing, shortness of breath, and chest tightness [1]. Globally, approximately 300 million individuals have asthma, of whom around 10% are classified as having severe asthma; the disease accounts for 1 in every 250 deaths worldwide [2].

Severe asthma is defined as "asthma which requires high-dose ICS plus a second controller and/or systemic corticosteroids to prevent a state of uncontrolled asthma or which remains uncontrolled despite treatment" [75]. However, the disease burden is the greatest in asthmatic individuals who remain symptomatic despite guideline-based treatment. Although this subset of patients accounts for only approximately 10% of the total population of asthma patients, they represent a substantial share of the consumption of healthcare resources including emergency department visits and hospitalization, and of unemployment and missed days or sick leave from work or school [3, 4]. In addition, they remain at risk of frequent exacerbations, increased morbidity and

mortality, and decreased quality of life [5–7]. This patient group may benefit from novel biological agents. However, these novel treatments necessitate the availability of reliable diagnostic tools for disease phenotyping, rendering the care of patients with severe asthma expensive. The novel biological drugs usually need to be injected, thereby requiring frequent visits to an outpatient clinic. Nevertheless, these patients could benefit substantially from a potential reduction in exacerbations.

The development of biological treatments for asthma was halted by early negative studies on the effect of anti-IL-5 and anti-IL-4 [8]. However, an increasing understanding of the existence of specific inflammatory phenotypes in asthma revived their development. By targeting anti-IL5 treatment to patients with eosinophilic asthma, it was possible to demonstrate a significant reduction in the number of exacerbations [9], whereas previous studies had not shown an effect. Similarly, the identification of a steroid responsive Th2 high gene expression profile [10] led to the development of periostin as a marker of Th2-activation, which subsequently enabled identification of a group of patients responding to anti-IL13 [11]. The majority of biological treatments under development target cytokines involved in Th2/type 2 inflammation, including, IL-5, IL-9, and IL-4/IL-13 [12, 13].

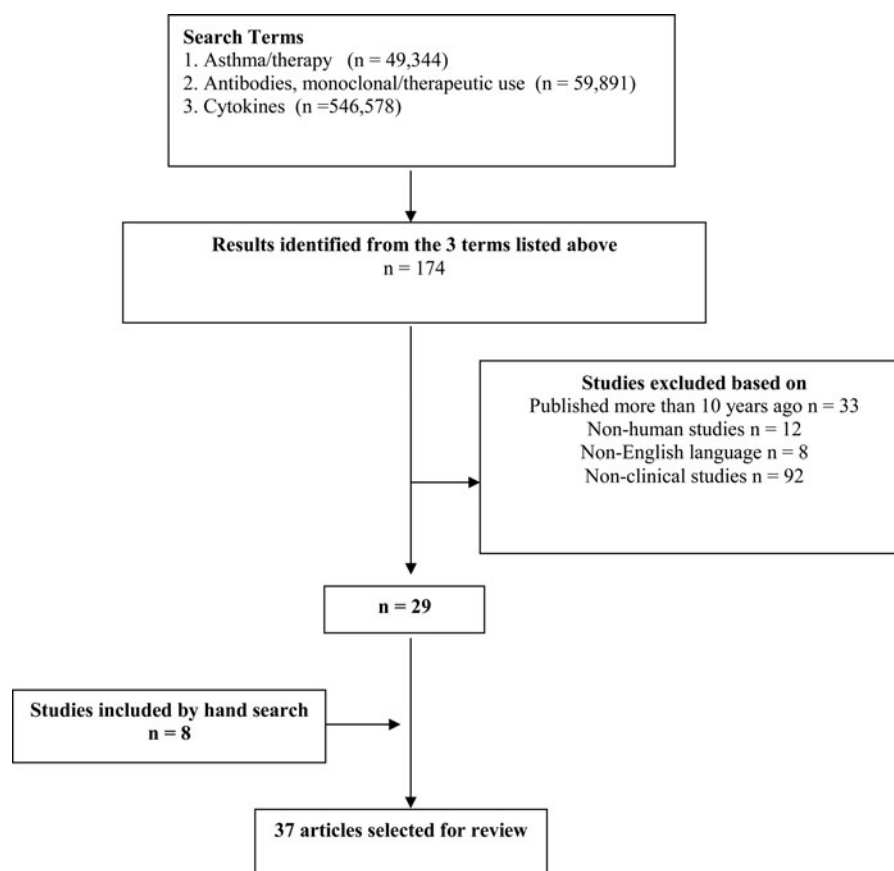


Figure 1. Flowchart for search strategy and study selection.

In this review, we discuss the currently available biological therapies as well as those under investigation to treat asthma. Additionally, we suggest perspectives for development.

Methods

A literature search was conducted between August and October 2016 using the PubMed database to identify published studies on biologics for add-on treatment of asthma. The following keyword algorithms were used: Asthma/therapy AND antibodies, monoclonal/therapeutic use AND cytokines. Asthma/therapy was used as a MeSH major topic, whereas the other two keywords were used as MeSH terms. This yielded 174 citations; subsequently, the search was limited to articles published in English. Review articles and animal studies were excluded; further, upon screening titles and abstracts, many were excluded because they i) dealt with lung diseases other than asthma, ii) grouped asthma together with other lung diseases, or iii) were not empirical studies. The citation pool was supplemented by hand searching through the bibliographies of excluded systematic reviews, and articles were retrieved from the reference list in relevant publications. A schematic representation of the study retrieval and selection is shown in Figure 1.

Results

The search identified 37 studies for review published in 2000–2016. Of these 37 studies, 5 were on the effects of anti-IgE (omalizumab); 12 on anti-IL-5; 8 on anti-IL-13; 5 on anti-IL-4R- α ; 3 on anti-IL-9; one on anti-TNF- α ; one on anti-IL-2; one on anti-TSLP; and one on anti-OX40L. All included clinical trials were randomized, double-blinded, and placebo-controlled apart from the omalizumab studies and one anti-IL-5 study, which were open-label. Sample sizes ranged from 3 to 943 participants. The search included 4 phase 1 studies: 3 concerning anti-IL-13 and one concerning anti-IL-5R- α . Studies of therapies targeting IgE, IL-2, IL-4R alpha, and IL-5 showed efficacy, whereas those targeting IL-9 and TNF- α lacked effectiveness. Omalizumab also had post-marketing studies, and these studies were therefore not placebo-controlled. Data from all studies are extracted and referenced in Tables 1–6. Unless otherwise stated, all the results represented are significant ($p < 0.05$).

Discussion

In this review, virtually all novel immunomodulating therapies were scrutinized. Overall, we found that

Table 1. Omalizumab (anti-IgE) studies.

Reference	Objective	Sample	Study	Treatment duration & administration	Findings
Shimizu [25]	To evaluate the influence of omalizumab therapy on asthma symptoms, lung function, episodes of exacerbation, and use of corticosteroids and SABAs.	9 patients with severe asthma. Mean age 63 ± 12.0.	Open-label study.	16 weeks 300 mg s.c. every 2 or 4 weeks.	Primary findings: Improvement in ACT score and morning PEF. Secondary findings: Increase in total IgE. No changes in neutrophil, eosinophil, basophil, and macrophage counts in induced sputum. No improvement in FVC, %FEV1 and V50/V25. Reduction in use of SABA and unscheduled hospital visits. Reduction in MIP1- δ and IL-16.
Zietkowski [26]	To assess changes in RANTES concentrations in EBC in asthmatic individuals with severe persistent allergic asthma during omalizumab therapy.	19 patients with severe persistent allergic asthma—omalizumab group (n = 9), mean age: 49.3 ± 8.2; control group (n = 10), mean age: 52 ± 8.6.	Open-label study.	16 weeks 150–375 mg s.c. every 2 or 4 weeks.	Primary findings: In the omalizumab group, a significant decrease was seen in 1) RANTES levels, 2) FeNO levels, 3) serum ECP levels, and 4) blood eosinophil count after treatment. Furthermore, a significant increase in FEV1 was observed in the omalizumab group. Secondary findings: Significant correlations between 1) the decrease in RANTES and decrease in FeNO, 2) decrease in serum ECP and decrease in FeNO, and 3) decrease in serum ECP and blood eosinophils were seen in the omalizumab group, but not in the control group.
Braunstahl [21]	To evaluate real-world effectiveness, safety, and use of omalizumab therapy.	943 patients with uncontrolled persistent allergic asthma. Mean age: 45 ± 12	International, single-arm, open-label, observational registry.	Up to 2-year follow-up. Specific dosages of omalizumab not stated.	Primary findings: Increase in the proportion of patients with no clinically significant exacerbations. Secondary findings: Reduction in asthma symptoms and improvement in asthma control (ACT, ACQ, and AQLQ-scores) and rescue medication use compared with baseline status. Increase in spirometric indices. Reduction in the use of oral corticosteroids.
Yalcin [31]	To evaluate the effect of omalizumab as treatment in patients with Samter's syndrome measured by serum ECP, IL-1 β , hs-CRP, and 25-hydroxyvitamin-D.	Pilot study of 3 patients with Samter's syndrome. Age range: 25–29 years	Observational study including 3 cases.	36-month follow-up 225–300 mg subcutaneous omalizumab every 2 weeks.	Primary findings: In all three patients, the levels of IgE, ECP, FeNO, soluble CD200, IL-1 β , and hs-CRP were decreased, while 25-hydroxyvitamin-D increased after treatment with omalizumab. Secondary findings: Allergic nasal symptoms and asthma symptoms decreased, but no change was seen in the development of nasal polyps.
Carciá [59]	To investigate whether omalizumab has biological and clinical effects in patients with refractory non-atopic asthma	41 adults randomized into a omalizumab group (n = 20), mean age: 55 ± 9.7 and a placebo group (n = 21), mean age: 54.6 ± 12.8.	Randomized double-blind, placebo-controlled, study.	16 weeks Dosages not stated, but determined by the European Summary of Product Characteristics.	Primary outcome: The median change in Fc ϵ RI expression on basophils and plasmacytoid dendritic cells (pDC2) decreased significantly in the omalizumab group compared to placebo in patients with severe nonatopic asthma. Secondary outcomes: A significant increase in FEV1 %predicted was observed in the omalizumab group compared to placebo. No significant changes were observed between the two groups in terms of cumulative numbers of exacerbation or ACO scores.

Table 2. Anti-IL-5 & anti-IL-5R α studies.

Reference	Objective	Sample	Study	Treatment duration & administration	Findings
Ortega [61]	To examine the effect of 75 mg i.v. and 100 mg s.c. mepolizumab (anti-IL-5) on asthma exacerbations in patients with either 150 cells/ μ L at screening or 300 cells/ μ L during the previous year.	580 patients were randomized into three groups; placebo (n = 191), mean age 49 (12–76), 75 mg mepolizumab (n = 191), mean age 50 (13–82), and 100 mg mepolizumab (n = 194), mean age 51 (12–81)	Phase 3, randomized, double-blind, double-dummy, placebo-controlled study.	32 weeks Treated with either 75 mg iv. or 100 mg s.c. every 4 weeks.	Primary outcome: The rate of exacerbations was reduced significantly by 47% and by 53% among patients receiving 75 mg iv. and 100 mg s.c. mepolizumab, respectively, compared to placebo. Secondary outcomes: FEV ₁ (ml), ACQ, and StGRQ scores were improved significantly in both treatment groups compared to placebo.
Nair [34]	To examine the prednisone-sparing effect of mepolizumab (anti-IL-5) and its effect on the number of eosinophils in sputum and blood, symptoms, and airflow limitation.	20 patients with persistent sputum eosinophilia randomized into: mepolizumab (n = 9), mean age: 56.9 $\pm$ 10.9 and placebo (n = 11), mean age: 58.2 $\pm$ 7.1.	Randomized, double-blind, placebo-controlled study.	20 weeks 750 mg iv. every 4 weeks.	Primary outcomes: A significant lower proportion of patients with exacerbations and a reduction in prednisone dose were seen in the mepolizumab group compared to placebo. Secondary outcomes: Blood and sputum eosinophils were significantly reduced. Improvement in ACQ scores.
Halder [9]	To study the effect of mepolizumab (anti-IL-5) for 12 months on the frequency of exacerbations in patients with refractory eosinophilic asthma.	61 patients were randomized into: mepolizumab group (n = 29), mean age: 48 (21–63) and placebo (n = 32), mean age: 50 (24–72).	Randomized, double-blind, placebo-controlled study.	50 weeks 750 mg iv. every month	No significant improvements in FEV ₁ . Primary outcome: Mepolizumab significantly reduced the frequency of severe asthma exacerbations. Secondary outcomes: Eosinophil count in the blood and sputum was significantly decreased. While improvement in quality of life was observed, no significant changes were seen in symptom score, post-bronchodilator FEV ₁ , or airway hyperresponsiveness.
Pavord et al. [35]	To assess if mepolizumab (anti-IL-5) reduces the frequency of asthma exacerbations and the effect on blood and sputum eosinophil counts, asthma control, asthma-related quality of life, and FEV ₁ .	621 patients were randomized into three treatment groups; 75 mg (n = 154), mean age: 50.2 $\pm$ 10.8 250 mg (n = 152), mean age: 49.4 $\pm$ 11.6 750 mg (n = 156), mean age: 48.6 $\pm$ 11.1, and placebo (n = 159), mean age: 46.4 $\pm$ 11.3.	Double-blind, placebo-controlled study	52 weeks 3 treatment groups; 75 mg iv. 250 mg iv. 750 mg iv.	Primary outcome: The frequency of asthma exacerbations was significantly decreased Secondary outcomes: In all three treatment groups, the time to first exacerbation was delayed significantly. Blood eosinophil counts were decreased significantly at all dosage, whereas sputum eosinophil counts were only decreased significantly in the 750-mg mepolizumab group. No significant improvements in FEV ₁ , AQLQ, and ACQ. The overall frequency of serious adverse events was similar across treatment groups.

Bjerner et al. [60]	To evaluate the effect of two different doses of reslizumab (anti-IL-5) , 0.3 and 3.0 mg/kg on FEV1 in patients with persistent asthma and elevated blood eosinophils (≥ 400 cells/ μ L).	315 patients randomized into three groups; reslizumab 0.3 mg/kg (n = 104), mean age: 44.5, 3.0 mg/kg (n = 106), mean age: 43.0 and placebo (n = 105), mean age: 44.2.	Phase 3, double-blind, placebo-controlled, parallel-group, fixed-dosage study.	16 weeks 2 treatment groups; 0.3 mg/kg iv. 3.0 mg/kg iv.	Primary outcome: FEV1 improved significantly in both dosage groups of reslizumab (0.3 and 3.0 mg/kg) compared to placebo. Secondary outcome: FVC improved significantly with 3.0 mg/kg reslizumab. Rescue inhaler use was reduced in both reslizumab groups compared to placebo. ACQ-5 and AQLQ improved significantly with 3.0 mg/kg reslizumab, but not 0.3 mg/kg or placebo.
Castro et al. [62]	To examine the efficacy and safety of reslizumab (anti-IL-5) in patients with inadequately controlled, moderate-to-severe asthma.	In two studies, 953 patients were randomized to receive i.v. reslizumab 3.0 mg/kg (n = 477), median age: 48 (37–57) and placebo (n = 476), median age: 48 (37–57).	Phase 3, two duplicate, multicenter, double-blind, parallel-group, randomized, placebo-controlled studies.	1 year 3.0 mg/kg iv. every 4 weeks.	Primary outcome: The annual frequency of asthma exacerbations was significantly reduced in patients treated with reslizumab compared to placebo. Secondary outcome: Reslizumab improved FEV1, ACQ, and AQLQ-scores, and blood eosinophil counts were reduced significantly compared to placebo.
Castro et al. [33]	To evaluate the effect of reslizumab (anti-IL-5) in patients with eosinophilic asthma that is poorly controlled with high-dose ICS.	106 patients were randomized to reslizumab (n = 53), mean age: 44.9 $\pm$ 13.9 and placebo (n = 53), mean age: 45.8 $\pm$ 11.7.	Randomized, double-blind, placebo-controlled study.	15 weeks 3.0 mg/kg iv. every 4 weeks.	Primary outcome: Reslizumab improved ACQ scores for patients with nasal polyps, but not in those without. Secondary outcomes: Reslizumab improved FEV1 reduced eosinophil sputum and blood counts. No effect on asthma exacerbations. Generally well-tolerated, most common adverse event was nasopharyngitis.
Lavolette [39]	To evaluate the safety of benralizumab (anti-IL-5Rα) and its effect on eosinophil counts.	27 patients were randomized; Cohort I: benralizumab (n = 8), mean age: 38.9 $\pm$ 14.7 and placebo (n = 5), mean age: 34.4 $\pm$ 9.7. Cohort II: benralizumab (n = 9), mean age: 38.9 $\pm$ 13.8 and placebo (n = 5), mean age: 40.2 $\pm$ 14.5.	Phase I, double-blind, placebo-controlled study.	8 weeks Cohort I: 1 mg/kg iv. on day 0. Cohort II: 100 or 200 mg s.c. on days 0, 28 and 56	Primary outcome: Benralizumab decreased the airway mucosal eosinophil counts compared to placebo 28 days after the last dose. Secondary outcomes: Eosinophils were not detectable in bone marrow of benralizumab-treated individuals. No serious adverse events related to benralizumab.

(Continued on next page)

Table 2. Continued

Reference	Objective	Sample	Study	Treatment duration & administration	Findings
Castro [63]	To assess the efficacy and safety of benralizumab (anti-IL-5Rα) in adults with uncontrolled eosinophilic asthma.	324 eosinophilic and 282 non-eosinophilic asthma patients were randomized into three treatment groups (n = 384) and placebo (n = 222). Mean age, eosinophilic: placebo 45.6 $\pm$ 11.7, benralizumab 47.16 $\pm$ 7.49* Mean age, non-eosinophilic: placebo 50 $\pm$ 12.3, benralizumab 50 $\pm$ 11.5 44 mild atopic asthmatic patients; 7 groups receiving escalating doses. Mean ages across the 7 groups: 21.3–28.1 (ranges: 18–41)	Phase 2b, randomized, controlled, double-blind, dose-ranging study.	1 year Eosinophilic: 2, 20 or 100 mg s.c. Non-eosinophilic: 100 mg s.c. Every 4 weeks the first 3 injections and then every 8 weeks.	Primary outcome: The annual exacerbation rate was reduced in patients with eosinophilic asthma, but the results did not reach statistical significance. Secondary outcomes: The reduction in exacerbation rate was significant for patients with baseline eosinophilic count $\geq$ 300 cells/ μ L. Nasopharyngitis and injection site reactions occurred more frequently in the treatment.
Busse [38]	To evaluate the safety profile, pharmacokinetics, and pharmacodynamics of MEDI-563 (anti-IL-5Rα) .		Phase 1, open-label, sequential dose-escalation study.	12 weeks Doses ranging from 0.0003 to 3 mg/kg iv. as single dose	Primary safety endpoint: The most frequently reported adverse events were reduced white blood cell counts and nasopharyngitis. Secondary findings: Mean peripheral blood eosinophil levels decreased in a dose-dependent fashion. ECP levels were reduced. Eosinopenia lasted at least 8 or 12 weeks depending on doses given.
Nowak [64]	To examine the effect of benralizumab (anti-IL-5Rα) on the recurrence after asthma exacerbation.	110 patients were randomized into benralizumab 0.3 mg/kg, mean age: 35.9 (20–60) and 1.0 mg/kg, mean age 34.8 (19–54), (n _{treatment groups} = 72), and placebo (n = 38), mean age 35.9 (22–55).	Phase 2, multicenter, randomized, double-blind, parallel group, placebo-controlled study.	84 days 1 dose of 0.3 or 1.0 mg/kg iv.	Primary outcome: The proportion of individuals with $\geq$ 1 asthma exacerbation at week 12 was not different between benralizumab and placebo. Secondary outcomes: Benralizumab reduced the rate and severity of exacerbations and eosinophil blood counts compared to placebo.
FitzGerald [69]	To assess the efficacy and safety of benralizumab (anti-IL-5Rα) as add-on therapy for patients with severe, uncontrolled asthma and elevated blood eosinophil counts ($\geq$ 300 cells/ μ L).	1306 patients were randomized to benralizumab every 4 weeks (n = 425), mean age 50 $\pm$ 13.6, every 8 weeks (n = 441), mean age 49 $\pm$ 14.3 and placebo (n = 440) mean age 48.8 $\pm$ 15.	Phase 3, multicenter, randomized, double-blind, parallel group, placebo-controlled study.	56 weeks 30 mg s.c. every 4 or 8 weeks.	Primary outcome: Benralizumab significantly decreased the annual exacerbation rate in both treatment groups compared to placebo. Secondary outcomes: Pre-bronchodilator FEV1 was significantly improved in both treatment groups, whereas significant improvements in ACQ scores were only observed in patients receiving treatment every 8 weeks.

* Average of mean age and standard deviations in the three treatment groups. SABA = short-acting-beta-2-agonist; EBC = eosinophil blood count.

Table 3. Anti-IL-13 studies.

Reference	Objective	Sample	Study	Treatment duration and administration	Findings
Hodsman [44]	To evaluate the safety, pharmacokinetics, and pharmacodynamics of different doses of GSK679586 (anti-IL-13) in a two-arm study; one including healthy individuals and one including patients with mild intermittent asthma	Healthy individuals were randomized to 5 treatment groups (n = 24), mean age: 24.4 ± 2.7 and placebo (n = 8), mean age: 26 ± 7. Asthma patients were randomized to 3 treatment groups (n = 21), mean age: 28.7 ± 5.1 and placebo (n = 7), mean age: 29 ± 6.	Phase 1, two-part, randomized double-blind, placebo-controlled study.	84 days The treated asthma patients received either 2.5, 10 or 20 mg/kg iv. twice 4 weeks apart.	Primary outcome: A dose-dependent pharmacological activity in the lungs of individuals with mild intermittent asthma was observed when treated with GSK679586. Secondary outcomes: Well-tolerated, no dose-related trends in AEs, with the exception of headache in asthma patients.
Singh [45]	To assess the pharmacokinetics, tolerability, and safety of repeated doses of CAT-354 (anti-IL-13) .	23 adults with mild-to-moderate asthma were randomized into three treatment groups with different dosages (n = 19), mean ages: 34.6 ± 7.6, 43.3 ± 14.5, 40 ± 13 and a placebo group (n = 4), mean age: 34.9 ± 9.1.	Phase 1, randomized, double-blind, placebo-controlled study.	21 weeks Treated with 3 doses of either 1.5 or 10 mg/kg iv. with 28 days intervals.	Primary findings: CAT-354 exhibited linear pharmacokinetics of all three dosages. Secondary outcomes: The half-life a single dose was 12–17 days with a low accumulation of the drug. All participants experienced at least one adverse event. The majority of the adverse events were considered mild to moderate and not related to the study drug.
De Boever [41]	To evaluate the efficacy and safety of the anti-IL-13 mAb (GSK679586) in patients with refractory asthma to maximally indicated dose of inhaled corticosteroids.	198 patients were randomized into a treatment group (n = 100), mean age: 51 ± 11 and a placebo group (n = 98), mean age: 51 ± 12.	Phase 2, randomized, double-blind, placebo-controlled study.	12 weeks 10 mg/kg iv. at day 1, week 4 and 8.	Primary outcome: No significant changes in ACQ-7 score were observed between the treatment and placebo groups. Secondary outcomes: No significant changes from baseline in FEV1 were observed. The incidence in exacerbation rate was similar in the intervention and placebo group.
Corren [71]	To determine whether treatment with lebrikizumab (anti-IL-13 mAb) would improve asthma control.	219 adults were randomized to lebrikizumab (n = 107), mean age: 45 ± 12 and placebo (n = 112), mean age: 44 ± 12.	Phase 2, randomized double-blind, placebo-controlled study.	24 weeks 250 mg s.c. was given monthly for 6 months.	Primary outcome: At week 12, the FEV1 was increased significantly from baseline in the lebrikizumab group compared to placebo. Secondary outcomes: Levels of FeNO decreased significantly in the lebrikizumab group compared to placebo. No significant changes were observed in overall exacerbation rate, the ACQ-5 score, asthma symptoms, and use of rescue medication between lebrikizumab and placebo.

(Continued on next page)

Table 3. Continued

Reference	Objective	Sample	Study	Treatment duration and administration	Findings
Noonan [42]	To investigate the efficacy and safety of lebrikizumab (anti-IL-13 mAb) in asthmatic, corticosteroid-naïve patients.	212 patients were randomized into four groups: 125 mg lebrikizumab (n = 54), 250 mg lebrikizumab (n = 54), 500 mg lebrikizumab (n = 52), and placebo (n = 52). Mean age of the total population: 39.7 ± 12.3.	Phase 2, randomized, double-blind, placebo-controlled, dose-ranging study.	12 weeks Either 12, 250 or 500 mg s.c. for a total of 4 doses over a 58-days period.	Primary outcome: Numerically higher change in FEV1 was seen in all three intervention groups, but did not reach statistically or clinically significance level. Secondary outcomes: Lebrikizumab was associated with a reduced risk of treatment failure at all doses compared with placebo.
Scheerens [43]	To evaluate the efficacy and safety of lebrikizumab (anti-IL-13 mAb) in patients with mild asthma who underwent bronchial allergen challenge.	29 patients were randomized into; a treatment group (n = 13), mean age: 36 ± 11 and a placebo group (n = 16), mean age: 32 ± 11.	Phase 2, multicenter, randomized, double-blind, parallel-group, placebo-controlled study.	12 weeks 5 mg/kg s.c. every 4 weeks, 4 doses in total.	Primary outcome: At the end of the study, late asthmatic response was reduced in the lebrikizumab group versus placebo, although not significantly. Secondary outcomes: Early asthmatic response was similar in the two groups. Levels of serum IgE, chemokine 13 and 17 were reduced significantly in the lebrikizumab group.
Piper [40]	To evaluate the effect of tralokinumab (anti-IL-13 mAb) on asthma control in adult patients with moderate-to-severe, uncontrolled asthma.	194 patients were randomized to three treatment groups (n = 146), mean age: 47.4 ± 11.1 and placebo (n = 48), mean age: 47.2 ± 9.8.	Phase 2a, multicenter, randomized, double-blind, parallel-group, placebo-controlled study.	12 weeks Treatment with either 150, 300 or 600 mg s.c. every 2 weeks.	Primary outcome: There was not significant difference in ACQ-6 scores between tralokinumb and placebo. Secondary outcomes: Tralokinumab tended to improve FEV1 ($p = 0.072$) and significantly reduced the use of rescue medication compared to placebo.
Brightling [65]	To assess the efficacy and safety of two dosing regimens of tralokinumab (anti-IL-13 mAb) in patients with severe asthma who have had 2–6 exacerbation in the previous year.	452 patients were randomized to receive tralokinumab every 2 weeks (n = 150), mean age: 49.7 ± 12.2 or every 4 weeks (n = 151), mean age: 50.5 ± 11.8 or placebo (n = 151), mean age: 50.3 ± 12.9.	Phase 2b, multicenter, randomized, double-blind, parallel-group, placebo-controlled study.	1 year 300 mg s.c. every 2 weeks or every 2 weeks for 12 weeks and hereafter every 4 weeks.	Primary outcome: Tralokinumab did not reduce the annual asthma exacerbation rate significantly compared to placebo. Secondary outcome: Subanalyses showed improvement in FEV1, ACQ-6, and AQLQ-scores in patients with high level of DDP-4 (Dipeptidylpeptidase-4) compared to placebo.

Table 4. Anti-IL-4 receptor alpha studies.

Reference	Objective	Sample	Study	Treatment duration and administration	Findings
Otulana [47]	To investigate the efficacy of dry powder inhalation formulation of pitracinra on the incidence in exacerbation rate in patients with uncontrolled, moderate-to-severe asthma.	534 patients were randomized into four groups; 1 mg (n = 132), 3 mg (n = 137), and 10 mg (n = 128) pitracinra group and placebo (n = 137). Patients $\geq$ 18 years of age were included.	Randomized double-blind, placebo-controlled study.	12 weeks Patients treated with either 1, 3, or 10 mg as inhaled dry powder.	Primary outcome: The study found no efficacy in the overall population; however, a significant reduction in exacerbation incidence was seen in a predefined subpopulation. Secondary outcomes: Improvements in symptom scores and spirometry in the subpopulation with eosinophilia, high FeNO, and GG genotype of the IL4R rs8832 SNP
Slager [48]	To test the hypothesis that amino acid changes in the 39 end of the IL-4 receptor, a gene (IL4RA) would predict reductions in asthma exacerbations in individuals randomized to pitracinra therapy.	534 participants with moderate-to-severe asthma from the intent-to-treat population were enrolled, mean age: 45.4 ± 13.7	Phase 2b, randomized, double-blind placebo-controlled study.	12 weeks Patients treated with either 1, 3, or 10 mg as inhaled dry powder twice daily for 12 weeks.	Primary outcome: No significant differences in exacerbations were seen between pitracinra and placebo. However, subanalyses showed that 10-mg pitracinra significantly decreased time to exacerbation among patients with rs8832GG genotype compared with placebo. Secondary outcomes: Individuals with the rs8832GG genotype treated with pitracinra in the low-eosinophil-count group only were less likely to have an exacerbation than those with the AG and AA genotype. A dose-dependent reduction in nocturnal awakenings was observed in patients with the rs8832GG and rs302462CC genotypes. (Continued on next page)

Table 4. Continued

Reference	Objective	Sample	Study	Treatment duration and administration	Findings
Wenzel [49]	To investigate whether Th2 immunity was important in a clinical setting where asthmatic individuals were experimentally challenged with aerosolised allergen after 4 weeks of treatment with pitirakinra .	Two independent studies; Study I: pitirakinra 25 mg (n = 12), mean age: 31 ± 10 and placebo (n = 12), mean age: 30 ± 9. Study II: pitirakinra 60 mg nebulization (n = 16), mean age: 25 ± 5 and placebo (n = 16), mean age: 29 ± 8.	2 independent, phase 2a, randomized double-blind, placebo-controlled study.	4 weeks Study I: 25 mg s.c. once daily. Study II: 60 mg nebulized twice daily.	Study I: There was a 17.1% and 23.1% maximum percentage decrease in FEV1 in the pitirakinra group vs. placebo, respectively, p = 0.243. Study II: There was a 4.4% vs. 15.9% average percentage decrease in FEV1 after allergen challenge in the pitirakinra group vs. placebo, respectively, p = 0.0001. Primary outcome: Asthma exacerbations occurred in 6% and 23% of the patients treated with dupilumab vs. placebo, respectively, p < 0.001. Secondary outcomes: In the dupilumab group, time to first exacerbation was prolonged, and the risk of exacerbation was reduced compared to placebo. Improvements in FEV1, morning PEF, ACQ-5 score, and reduction in the use of rescue medication were. Injection site reactions, nasopharyngitis, nausea, and headache occurred more frequently in the dupilumab group.
Wenzel [50]	To evaluate the efficacy and safety of dupilumab (anti-IL-4R alpha) in patients with persistent, moderate-to-severe asthma with eosinophilia.	104 patients with persistent, moderate-to-severe asthma: a dupilumab group (n = 52), mean age: 37.8 ± 13.2 and a placebo group (n = 52), mean age: 41.6 ± 13.1.	Phase 2a, randomized, double-blind, placebo-controlled study.	12 weeks 300 mg s.c. once weekly.	Primary outcome: Patients treated with dupilumab every 2 weeks, but not every 4 weeks improved in FEV1 compared to placebo. The improvement was significant regardless of blood eosinophil counts. Secondary outcomes: The annualized exacerbation rate was significantly lower in patients treated with dupilumab every 2 weeks, but not every 4 weeks compared to placebo.
Wenzel [70]	To assess the efficacy and safety of dupilumab (anti-IL-4R alpha) as add-on therapy in patients with uncontrolled, persistent asthma on medium-high-dose inhaled corticosteroids + long-acting beta-2-agonist.	769 patients were randomized to dupilumab groups, 200 or 400 mg every 2 or 4 weeks (n = 611) and placebo (n = 158). Mean age in the overall population: 48.6 ± 13.	Phase 2b, randomized, double-blind, placebo-controlled study.	12 weeks Treatment with either 200 or 300 mg every 2 or 4 weeks, thus 4 different treatment groups.	Primary outcome: Patients treated with dupilumab every 2 weeks, but not every 4 weeks improved in FEV1 compared to placebo. The improvement was significant regardless of blood eosinophil counts. Secondary outcomes: The annualized exacerbation rate was significantly lower in patients treated with dupilumab every 2 weeks, but not every 4 weeks compared to placebo.

Table 5. Anti-IL-9, anti-TNF- α and anti-IL-2R- α studies.

Reference	Objective	Sample	Study	Treatment duration and administration	Findings
Parker [51]	To assess the safety profile and potential efficacy of multiple subcutaneous doses of MEDI-528 (anti-IL-9) .	<i>Study 1:</i> 36 patients with mild asthma randomized to three MEDI-528 groups (n = 27), combined mean age: 33.4(18–61) and placebo (n = 9), mean age: 38.6(22–63). <i>Study 2:</i> 11 patients with mild-to-moderate asthma randomized to MEDI-528 (n = 7), mean age: 32.1(19–39) and placebo (n = 4), mean age: 31.8(19–47).	Phase 2a, randomized double-blind, placebo-controlled study.	4 weeks Patients received either 0.3 mg/kg s.c. or 1 mg/kg s.c. or 3 mg/kg s.c. twice weekly.	Primary outcome: Participants tolerated multiple SC doses of MEDI-528, with AE and SAE rates similar to placebo. No persons developed anti-MEDI-528 antibodies. Secondary outcomes: No effect on lung function. A trend toward improvement in the overall mean asthma symptom scores during the treatment period in all participants compared with baseline value. Primary outcome: No effect on early asthmatic response or late asthmatic response. Secondary outcomes: No significant reduction in FeNO. A trend toward improvement in AHR. AEs were mild to moderate and similar between the two groups.
Gauvreau [53]	To evaluate the effects of medi-528 (anti-IL-9) on inhaled allergen responses.	30 patients with mild asthma randomized to MEDI-528 group (n = 15) and placebo (n = 15).	Phase 2a, randomized double-blind, placebo-controlled study.	8 weeks Patients received 9 mg/kg iv. as a single dose.	Primary outcome: No effect on early asthmatic response or late asthmatic response. Secondary outcomes: No significant reduction in FeNO. A trend toward improvement in AHR. AEs were mild to moderate and similar between the two groups.
Oh [54]	To evaluate the effect of MEDI-528 (anti IL-9) in adults with uncontrolled moderate-to-severe asthma.	329 patients were randomized to one of three treatment groups (n = 245), combined mean age: 42.8 $\pm$ 11.7 and placebo (n = 82), mean age: 43.6 $\pm$ 11.6.	Phase 2b, randomized, double-blind, placebo-controlled, parallel group study.	24 weeks Patients treated with either 30 mg s.c. or 100 mg s.c. or 300 mg s.c. every 2 weeks.	Primary outcome: There was no significant difference in ACQ-6 scores between the two groups. Secondary outcomes: No significant differences between exacerbation rates or changes in FEV1 in the treatment groups vs. versus placebo. (Continued on next page)

Table 5. Continued

Reference	Objective	Sample	Study	Treatment duration and administration	Findings
Wenzel [55]	To assess the safety and efficacy of multiple subcutaneous injections of golimumab , (anti TNF-α).	309 individuals with uncontrolled, severe persistent asthma were randomized to three golimumab groups ($n = 231$), combined mean age: 50.4 ± 7.03 , and placebo ($n = 78$), mean age: 49.4 ± 12 .	Phase 2, randomized, double-blind, placebo-controlled study.	52 weeks Patients treated with either 50 mg s.c. or 100 mg s.c. or 200 mg s.c. every 4 weeks.	Primary outcome: No significant differences changes in %FEV1 or severe exacerbations between treatment and placebo. Secondary outcomes: SAEs occurred more frequently in the golimumab groups than in the placebo group. One death and all eight malignancies occurred in the active groups.
Busse [56]	To evaluate the safety and efficacy of daclizumab (anti-IL-2R α).	115 patients with moderate-to-severe persistent asthma were randomized 3:1 to daclizumab ($n = 88$), mean age: 43.2 ± 12.5 and placebo ($n = 27$), mean 41 ± 12.4 .	Randomized double-blinded, placebo-controlled study.	20 weeks Patients treated with 2 mg/kg iv. every 2 weeks.	Primary outcome: Improvement in FEV1 was seen in the daclizumab group. Secondary outcome: Daytime asthma symptoms, the use of SABA, and blood eosinophil counts were reduced, while time to exacerbation was delayed in the treatment groups. Adverse events were evenly distributed between groups, although there were more serious adverse events in the daclizumab group.

Note. AE = adverse event; SAE = serious adverse event.

Table 6. Anti-TSLP and anti-OX40L.

Reference	Objective	Sample	Study	Treatment duration and administration	Findings
Parker et al. (43)	To assess the safety profile and potential efficacy of multiple subcutaneous doses of MEDI-528 (anti IL-9)	<i>Study 1:</i> 36 patients with mild asthma – medi-528 (27), placebo (9) <i>Study 2:</i> 11 patients with mild-to-moderate asthma – medi-528 (7), placebo (4)	Randomize double-blind, placebo- controlled study	4 weeks	Subjects tolerated multiple SC doses of MEDI-528, with AE and SAE rates similar to placebo group. No subjects developed anti-MEDI-528 antibodies. No effect on pulmonary function. A trend toward improvement in the overall mean asthma symptom scores during the treatment period in all subjects compared with baseline value. Decrease in FEV1 after allergen challenge was significantly smaller in the AMG157 group than in the placebo group. Primary outcome: Secondary outcomes: There was a significant decrease in level of blood and sputum eosinophils and in FeNO before and after allergen challenge in the intervention group.
Gauvreau et al. [57]	To evaluate the effect of AMG157, an anti-TSLP on late asthmatic response as measured 3–7 hours after allergen challenge.	31 patients randomized to receive AMG157 (n = 16), mean age: 30.8 ± 2.7 and placebo (n = 15), mean age: 31.5 ± 2.9.	Proof-of-concept, randomized double-blind, placebo-controlled study.	12 weeks Patients treated with 700 mg iv. on days 1, 29 and 57.	Primary outcome: Secondary outcomes: There was a significant decrease in level of blood and sputum eosinophils and in FeNO before and after allergen challenge in the intervention group.
Gauvreau et al. [58]	To test whether the effect of anti-OX40L mAb would inhibit allergen-induced responses in individuals with asthma.	28 patients were randomized to either anti-OX40L mAb (n = 14), mean age: 33.4 ± 13.3 or placebo (n = 14), mean age: 33.9 ± 12.0.	Phase 2b, randomized double-blind, placebo-controlled study.	3 months Loading dose of 8 mg/kg iv. and then 4 mg/kg iv. on days 29, 57 and 85.	Primary outcome: Anti-OX40L mAb did not have an effect on allergen-induced airway responses. Secondary outcomes: Anti-OX40L mAb showed no effect on AHR or blood eosinophils was observed. Total IgE and sputum eosinophils decreased significantly in the intervention group compared to placebo.

Table 7. Predictors and expected clinical outcomes in anti-Th2-targeted treatment.

Cytokine	Biomarkers	Clinical outcomes	
IgE	Atopy (positive skin prick test)	↓ Symptoms	↑ Lung function
	↑ Total IgE	↓ Exacerbations	↑ Quality of life
	↑ Allergen specific IgE	↓ Dose of ICS	
IL-5/IL-5R- α		↓ Health care utilization	
	History of asthma exacerbations	↓ Exacerbations	
	Steroid resistance	↓ Prednisone	
	↑ Blood and sputum eosinophils	↓ Health care utilization	
	↑ FeNO	↓ Symptoms	
IL-4/IL-13	Nasal polyps (IL-5R- α)	↑ Lung function (IL-5R- α)	
	↑ Serum periostin	↑ Lung function	
	↑ FeNO		
	↑ Blood and sputum eosinophils		
	↑ IL-13 I sputum	↑ Lung function Only in the subpopulation	
	↑ DDP-4 (Dipeptidylpeptidase-4) (tralokinumab)	↓ Symptoms	with ↑ DDP-4

For the remaining, Th2 cytokines data are too insufficient to suggest possible predictors of response.

these therapeutic options could be a suitable alternative for patients with refractory asthma, but based on current results, firm conclusions cannot be drawn on all cytokines. Further research is required, perhaps coupled with better phenotyping. In the following, we discuss the current therapeutic options, starting with omalizumab, as this agent is well established on the market and is available for prescription, followed by anti-IL-5 treatment, which was approved for treatment recently and lastly, we consider the scope of the remaining therapies.

Omalizumab

Omalizumab is a recombinant humanized anti-IgE antibody that binds to IgE and thereby decreases the amount of free IgE molecules and subsequently prevents the binding of IgE to receptors on inflammatory cells such as mast cells, resulting in reduced degranulation and release of inflammatory mediators.

Omalizumab (Xolair®; Genentech/Novartis) was the first approved immunomodulator for allergic asthma patients. The safety and efficacy as an add-on therapy has shown significant results in clinical trials investigating patients with moderate-to-severe uncontrolled asthma [14–18]. The effect of omalizumab includes reduction in exacerbation rates, fewer emergency visits, less need for systemic steroid, and improvement in asthma symptoms and asthma-related quality of life. In addition, a substantial improvement in comorbidities, such as allergic rhinitis, has been found as a positive side effect [19, 20] (Table 1).

The results from the randomized clinical trials indicate a significant effect of omalizumab in the treatment of severe asthma. These results were supported by The eXperience Registry, a 2-year real-life study of omalizumab treatment in severe asthma patients [21]. Moreover, similar results have been found in other long-term observational studies, indicating that the clinical

outcomes can be transposed to real-life settings [19, 22, 23]. The strength of these studies lies in the large number of patients and long study duration. The percentage of patients with no clinically significant exacerbations was 54.1% at month 12 and 67.3% at month 24. Among patients receiving OCS at baseline, there was a reduction in OCS dose or discontinuation of OCS treatment in 57.1% and 69.0% of patients at months 12 and 24, respectively [18].

Three articles in our search investigated immunological changes after treatment with omalizumab, suggesting that the clinical benefit also can be attributed to the decrease in production of IL-5, reduction of IL-16, and in RANTES levels [24–26]. These studies included a small number of patients only and are insufficient to clearly prove the findings, but they are examples of the kind of study that could provide further knowledge concerning the immunological effect of anti-IgE therapy. Given the high clinical effectiveness of the drug, as much insight as possible into the underlying mechanism is essential, and since it is the most used biological agent, the selection process of patients for treatment and assessment of outcomes should be systematic and consistent, thus setting a standard for future therapy protocols. However, this requires better phenotyping, which could predict the patients most likely to respond to omalizumab based on baseline characteristics. One of these possible biomarkers could be FeNO, eosinophilia, or periostin [27]. Studies show that the efficacy of omalizumab is unaffected by baseline serum IgE [14, 28], while FeNO, peripheral blood eosinophil counts, and serum periostin may be more useful in identifying the patients [25]. Follow-up on clinical outcomes has been debated, one could be exacerbation, but might not be sufficient as clinical tool, whereas Asthma Control Questionnaire (ACQ), Asthma Symptom Tracker (AST), or others alone are difficult as patients might keep the symptom score but reduce the level of ICS treatment [29]. The most precise method

of predicting a continuing persistent response to omalizumab is the physician's overall assessment of response (GETE) after 16 weeks of treatment [29], which currently also appears to be the most commonly used criterion [19, 21]. The high cost, ranging from \$500 to \$2000 for dosing every 4 weeks [30], and inconvenience for patients receiving omalizumab treatment merely underline the importance of targeted therapy. An unelaborated area of previous studies is defining and characterizing the non-responders to omalizumab treatment, defined after 4 months of treatment, which is essential for determining the patients who could benefit from the treatment. Data from the studies collectively indicate that non-responders account for approximately one-quarter of those treated, but no identification of this group is provided [19, 21, 29].

Moreover, subgroup analyses by Hanania et al. [27] showed that the effect of omalizumab seemed not to be present in patients treated with oral corticosteroids. These findings are consistent with a real-life study with adult asthmatic individuals [22] and a Cochrane review with both children and adults [66].

Thus, in order to increase the success of treatment of patients with severe asthma, the physician should determine whether the patient meet following criteria; elevated total serum IgE, allergen specific IgE, high blood eosinophils, or serum periostin or FeNO.

Furthermore, one study showed that patients with confirmed Samter's syndrome (asthma, aspirin intolerance and nasal polyps) improved in lung function, reduced their use of OCS, were reduced in levels of FeNO and laboratory markers (serum ECP, hs-CRP, eosinophils and IgE) when treated with omalizumab [31].

The early clinical trials reported a small increased risk of malignancies; however, a pooled analysis showed no association between omalizumab treatment and risk of malignancies [76]. Finally, the recent EXPECT study evaluated maternal-, pregnancy- and infant-related outcomes after exposure to omalizumab and reported the prevalence of these outcomes to be no higher than those reported in the general asthma population [32].

Anti-IL-5

IL-5 is a cytokine involved in the replication and maturation of eosinophils in the bone marrow as well as the later processes in the inflammatory response with its receptor, IL-5R α found on eosinophils and some basophils [67]. While mepolizumab and reslizumab act as IL-5 inhibitors, benralizumab is an antibody that specifically binds the receptor alpha subunit on the target cell.

Mepolizumab (Nucala[®]; GlaxoSmithKline) was the first anti-IL-5 monoclonal antibody approved for clinical use in the end of 2015. While mepolizumab seems to convincingly reduce the asthma exacerbation rate, the

effect on FEV1 or asthma symptoms has not been significantly different from placebo. However, reslizumab has shown a significant reduction in asthma exacerbation rate, improvement in FEV1 and asthma symptoms, particularly in patients with nasal polyposis.

Benralizumab, an anti-interleukin-5 directed against the α -chain of the receptor, has demonstrated an acceptable safety profile, effectively lowered peripheral blood eosinophil counts, and has recently been shown to significantly decrease asthma exacerbation rates and improved FEV1 and asthma symptoms (Table 2).

Anti-IL-5 appears to be a promising potential therapeutic option as studies of severe asthma suggest that one-half to two-thirds of the patients have persistent eosinophilia in the main airway, and the presence of eosinophils is related to higher risk of exacerbations, near-fatal events, and lower FEV1 compared with subtypes without eosinophils [36]. In the study by Haldar et al. [9], the authors reported a decrease in exacerbation rate and increased asthma-related quality of life, which supports previous studies showing a significant association between asthma exacerbations and health-related quality of life. Outcomes after cessation of 12-month treatment with mepolizumab in a 12-month follow-up showed a significant increase in overall exacerbation rate and in blood eosinophils, indicating that, like omalizumab, mepolizumab is a temporary treatment without the ability to cure. A significant increase in sputum eosinophils was seen after 3-month cessation but not thereafter [37].

Clinical studies on mepolizumab and reslizumab add to the growing body of evidence that identifying unique phenotypes associated with response is critical for optimizing the clinical benefit of treatment. Studies on mepolizumab showed that sputum eosinophilia at inclusion was associated with a reduced risk of asthma exacerbation, number of sputum and blood eosinophils, and doses of required corticosteroids [9, 34], and the severity of the exacerbation in terms of dosages of required corticosteroids and hospitalization was also reduced [35].

Previous studies on mepolizumab did not find improvements in FEV1 or asthma symptom scores, suggesting that these parameters can be disassociated from eosinophilic inflammation [9, 35].

However, recent studies have shown that in patients with severe eosinophilic asthma, mepolizumab both reduced the exacerbation rate and improved FEV1 and asthma symptom scores [61]. Eosinophilic asthma was defined as eosinophil blood count of at least 150 cells/ μ L at screening or at least 300 cells/ μ L during the previous year. These findings were echoed by a systemic corticosteroid-sparing study, showing mepolizumab decreased the daily doses of corticosteroids, improved asthma control, and FEV1 [68].

In a 15-week study, reslizumab decreased both sputum and eosinophil counts, and improved FEV1 and ACQ scores in patients with elevated baseline sputum and blood eosinophil counts. Interestingly, the improvement in ACQ-score was only significant in patients with nasal polyposis [33].

To fully elucidate this association and to determine whether the presence of nasal polyposis may help detect patients for whom the anti-IL-5 therapy is efficacious, future studies specifically designed to examine the association are needed.

The effect of reslizumab was also demonstrated in two other independent large and recent studies [60, 62]. In a 16-week study in patients with persistent eosinophilic asthma (eosinophil counts ≥ 400 cells/ μ L), reslizumab improved FEV1, ACQ-5, and Asthma Quality of Life Questionnaire (AQLQ)-score in two different subcutaneous doses of reslizumab compared to placebo [60], and in another study of patients with uncontrolled moderate-to-severe asthma, reslizumab decreased the annual frequency of asthma exacerbations, and improved FEV1, ACQ and AQLQ-scores significantly compared to placebo [62].

Benralizumab, a monoclonal antibody directed against the α -chain of IL-5R, demonstrated an acceptable safety profile and significantly decreased eosinophil blood counts in early trials [38, 39]. In recent large studies, the effect of benralizumab on annual exacerbation rates in patients with eosinophilic asthma was assessed [63, 64, 69]. In the two studies defining eosinophilia as ≥ 300 cells/ μ L, a significant reduction in exacerbation was observed in the benralizumab group compared to placebo [63, 69], but in another trial using a cutoff value of ≥ 450 cells/ μ L, the proportion of individuals ≥ 1 exacerbations at week 12 was similar in the treatment group and placebo [64]. However, the exacerbation rate was significantly lower in the benralizumab group compared to placebo [64]. It is unknown whether blocking of the IL-5R- α will result in the same changes in clinical outcomes when the blocking is targeted IL-5.

Overall, these findings support preselection of a specific patient population with a history of asthma exacerbations, sputum and blood eosinophils, and steroid resistance as a method to increase the utility of mepolizumab treatment in patients with severe asthma.

Anti-IL-13

IL-13 increases goblet cells hyperplasia, enhances bronchial hyperresponsiveness, and stimulates the B cell to produce IgE and migration of eosinophils into the lungs [71].

8 studies on anti-IL-13 were identified, including phase 1, phase 2a, and 2b studies. The early safety studies showed an acceptable safety profile. Two phase 2 studies assessed the effect of lebrikizumab on FEV1; one reported a significant increase compared to placebo, while the other did not find statistically or clinically significant changes between lebrikizumab and placebo.

There were two studies evaluating the effect of tralokinumab; a phase 2a study reported no statistical improvement in asthma symptoms score or FEV1, while a recent phase 2b study found statistically significant improvement in both asthma symptom scores and FEV1 in a subgroup of high level of dipeptidylpeptidase-4 compared to placebo (Table 3). Results from studies on treatment with interleukin-13 antibodies show the heterogeneous nature of asthma and raise the matter of stratification of patients according to an expected phenotype.

In the phase 1 study evaluating the safety and efficacy of GSK679586, De Boever et al. [41] measured serum total IL-13 from baseline in both the intervention and placebo groups, and the authors found no clinically or statistically significant improvement in asthma symptoms, lung function, or exacerbation rate. Neither did Noonan et al. [42] find any improvement in lung function, but they found that the treatment group had a reduced risk of treatment failure with no apparent difference between doses of lebrikizumab. Although not significant, Scheerens and colleagues found in a phase 2 study that the lebrikizumab group had a 48% reduction in late asthmatic response. Through exploratory analysis, they found that the asthmatic individuals with elevated baseline levels of blood eosinophils, serum IgE, or periostin exhibited a greater reduction in late asthmatic response compared with individuals with low levels of these biomarkers at baseline [43].

Furthermore, the improvements in lung function in studies with tralokinumab [40] and lebrikizumab [11] were more pronounced in individuals with higher IL-13 sputum levels and higher FeNO or periostin levels, respectively, indicating that these biomarkers could be highly valuable in predicting the magnitude of response to the specific therapy. FeNO, sputum, or blood eosinophil was not included as an end point in a phase 2a tralokinumab study [40].

The overall results from these phase 2 studies were not overly convincing, but as Piper and colleagues [40] suggest, the treatment effects could have been lowered by the presence of persons who lacked the potential to respond to tralokinumab, given that the authors did not account for the presence or absence of elevated IL-13 in the study population at baseline. Moreover, outcomes such as asthma symptom scores or exacerbation rates may

have been limited by the duration of the study of 12 and 24 weeks for tralokinumab and lebrikizumab, respectively.

However, in another larger and longer trial, talokinumab did not affect the exacerbation rate, but significant improvements in lung function and ACQ-6 scores were observed [65]. Subgroup analyses showed that the benefits of tralokinumab were greatest in patients with high DPP-4 (Dipeptidylpeptidase-4) and periostin levels. These results could be used in the stratification and preselection of patients to be treated with tralokinumab. The safety and efficacy of tralokinumab in patients with uncontrolled asthma are being investigated in ongoing phase 3 trials with different outcomes (ClinicalTrials.gov numbers NCT02194699, NCT02281357, and NCT02161757).

Long-term safety assessments should be undertaken because while phase I studies of anti-IL-13 demonstrated an acceptable safety profile [44, 45], the frequency of adverse events in the phase II study of tralokinumab was higher in the treated population [40]. A 52-week study evaluating the effect of lebrikizumab on patients with uncontrolled, severe asthma is underway (Clinical-Trial.gov identifier: NCT01868061).

Anti-IL-4R- α

IL-4 is involved in both upregulation of IgE receptors on the cell surface and secretion of IgE [72], activation of mast cells [73], mucus hypersecretion, and differentiation of T-helper cells into Th-2 cells [74]. So far, studies on pitrakinra and dupilumab have been published. The results from the pitrakinra studies indicate that only a subpopulation with rs8832GG genotype of the IL-4R of the included asthma patients had benefit. The 12-week phase 2a study on dupilumab showed that exacerbations occurred in 6% and 23% of the patients treated with dupilumab vs. placebo, respectively, $p < 0.001$. The recent large, phase 2b study showed that dupilumab in three out of four treatment regimens increased FEV1 significantly compared to placebo regardless of blood eosinophil counts. The annualized severe asthma exacerbation rate was also significantly decreased in patients receiving dupilumab every 2 week, but not every 4 weeks compared to placebo (Table 4).

Pitrakinra and dupilumab target allergic Th2 inflammation through inhibition of the alpha subunit of the IL-4 receptor, a signaling component of the heterodimeric receptor complex for both IL-4 and IL-13 [46]. The study population in these trials was also patients with moderate-to-severe asthma. Two studies with pitrakinra failed to reduce asthma exacerbation rates in the whole study population, but using genetic variation as a biomarker identified subgroups that showed improvement in patients homozygous for the rs8832GG allele

[47], and eosinophilic and upper tertile FeNO subgroups [48]. One of the studies included lung function measurements and change in daily use of beta2-agonist reliever as secondary endpoints, but no effects on these were observed [47].

In two independent phase 2a clinical trials in patients with atopic asthma, Wenzel and colleagues demonstrated that 25 mg subcutaneous pitrakinra had no significant effect in maximum change in %FEV1 after allergen challenge compared to placebo. However, administration of 60-mg nebulized pitrakinra was associated with a significant lower average decrease in %FEV1 compared to placebo (4.4% vs. 15.9%) after allergen challenge [49].

In a population of asthma patients with eosinophilic asthma, defined as ≥ 300 cells/ μ L, dupilumab had a significant effect on the risk of exacerbations during down titration of steroid and bronchodilator treatment. Furthermore, dupilumab treatment resulted in significant improvements in both lung function and asthma control [50]. The importance of IL4/IL-13 antagonism has been reinforced, but the real clinical value is still uncertain, given the specific and limited range of responders, and more importantly, the fact that the positive results were seen only during ICS and LABA withdrawal [50], thus not reflecting their effect as add-on therapies.

However, the latter issue was addressed in a large and recent phase 2b study, which demonstrated a significant increase in FEV1 in eosinophilic (≥ 300 cells/ μ L) asthma patients treated with dupilumab (every 2 or 4 weeks) compared to placebo with the greatest increases in those receiving treatment every 2 weeks. The annualized exacerbation rate was significantly decreased in the subgroups receiving treatment every 2 weeks, but not every 4 weeks compared to placebo. Interestingly, the benefits of dupilumab every 2 weeks were also present in patients with eosinophil blood counts ≤ 300 cells/ μ L.

A 52-week, phase 3 trial evaluating the effect of dupilumab on reducing asthma exacerbation rate is ongoing (ClinicalTrials.gov identifier: NCT02414854).

Anti-IL-9

In the two-trial randomized phase 2a study on the safety and efficacy of the humanized anti-IL-9 monoclonal antibody, MEDI-528 reported no changes in lung function [51]. The authors reported a trend toward improvement in the overall mean asthma symptom scores; however, these changes were less than 0.5, which is the conventional cutoff value for a minimal important difference with a clinical relevance [52]. The study showed a possible reduction in airway hyperresponsiveness, but due to the small sample size in both studies and study duration, no firm conclusions can be drawn. Gauvreau et al.

[53] also evaluated the efficacy of MEDI-528, where a similar trend toward improvement in AHR was reported, but no changes in FeNO as a biomarker of inflammation were observed. Anti-IL-9 therapy represents a possible approach for treating patients with asthma, but the clinical results to date are not convincing. In a larger and prolonged phase 2b study with 247 patients randomized into four groups: placebo and three different doses of MEDI-528, after 24 weeks of treatment, Oh and colleagues did not find any improvement in ACQ-6 scores, exacerbation rates, or FEV1 [54].

TNF- α

Tumor necrosis factor- α has shown to be relevant in asthma because elevated levels of this cytokine have been observed in induced sputum from asthmatic patients. Data from a large study of patients treated with golimumab indicate that it is not effective in patients with persistent, severe asthma, and an unfavorable risk-benefit profile with significant side effects resulted in early discontinuation of the drug. However, post-hoc analysis indicated that golimumab reduced risk of exacerbation in patients with FEV1 reversibility of 12% or more, or with a history of sinusitis [55]. Overall, given the poor results of efficacy and serious side effects, this drug will most likely not be investigated for asthma treatment in the future.

Anti-IL-2

Daclizumab is a humanized monoclonal antibody that binds specifically to the α -subunit of the IL-2 receptors on T lymphocytes, thus inhibiting the activation and biological function of these cells. Its use in patients with moderate-to-severe asthma led to significant improvements in lung function and asthma control [56]; however, these changes were not maintained during tapering of ICS use. Daclizumab is administered intravenously, which makes it impractical for regular use. Although the results of this pilot study are positive, long-term efficacy and especially safety should be further assessed as the inhibition level occurs at an earlier stage of the immunological process, which in the long run could lead to a higher risk of severe infections.

Anti-TSLP and anti-OX40L

Thymic stromal lymphopoietin is an epithelial-cell-derived cytokine that is thought to be involved in initiating a Th2-type inflammation. In a proof-of-concept study by Gauvreau and colleagues, 31 individuals with mild asthma were randomized to receive three monthly doses of anti-TSLP, AMG157, or placebo. Allergen challenge

was performed on Days 42 and 84, and the maximum percentage decrease in FEV1, FeNO, and blood and sputum eosinophils was measured; the authors found a significant decrease in all measurements. AMG157 displayed an acceptable safety profile [57].

Although only one study has been published on anti-TSLP, these findings indicate a key role of TSLP in allergen-induced airway response and initiation of inflammation. Targeting the TSLP-cytokine is interesting due to its site of action and early initiation in the Th2 immune response and could possibly have a significant effect on the downstream cytokines involved in allergic airway inflammation. The effect of AMG157 is further examined in two ongoing phase 2 studies (ClinicalTrials.gov identifier: NCT02698501 and NCT02237196).

In another study by Gauvreau and colleagues, they evaluated whether an anti-OX40L monoclonal antibody would inhibit allergen-induced responses in asthmatic individuals. The OX40L/OX40L interaction is thought to play an important role in optimal T cell response. They found no difference in early or late asthmatic response in the anti-OX40L group vs. placebo. However, serum IgE and sputum eosinophils were reduced significantly in the treatment group vs. the placebo group [58].

Conclusion and future perspectives

In order to meet the immense challenge of asthma management with tailored therapy and the marked heterogeneous pathogenesis of the disease, a great deal of research has been conducted. These studies have found a number of novel biological agents that appear to be relevant for asthma patients whose asthma is inadequately controlled despite standard treatment including but not limited to anti-IgE, anti-IL-5, and anti-IL-13. This review shows how profiling and phenotyping of patients with severe asthma are becoming increasingly important for the development of these therapies as it seems that they may be more helpful in carefully selected subsets of patient populations. However, these novel treatments will also necessitate the availability of reliable diagnostic tools for disease phenotyping. Indeed, both genotypic and phenotypic subclassifications have the potential to guide our clinical decision-making, exemplified by therapies targeting IL-5, IL-13, and IL-4R α , which all succeeded in identifying subgroups of asthma patients in which these monoclonal antibodies have significant benefit. It is essential that we acknowledge that specific therapies will most likely not have effect in all individuals. The variability of the responses to these novel interventions merely emphasizes the need for a personalized therapeutic approach in asthma management. In uncovering possible predictors of better treatment response, the use of

biomarkers, such as sputum and blood eosinophil counts, FeNO, sputum cytokine levels, or serum periostin, has yielded positive results (Table 7). Nevertheless, it remains to be established whether these biomarkers, separately or in combination, will be appropriate for regular clinical use.

A substantial number of patients with severe allergic asthma have benefitted from the approval of omalizumab, but further studies aiming to clarify characteristics of responders and non-responders, and thereby identifying predictors of treatment response, are needed.

Anti-IL-5 therapy is the most recently approved drug for patients with severe asthma with evident eosinophilic inflammation. The identification of asthma endotypes in the past years together with the growing palette of phenotypes might be the source to a more comprehensive understanding of disease mechanism, thereby enabling development of future biological treatments.

Just as corticosteroids have become the gold standard treatment for asthma, individually tailored therapy has the potential to achieve the same status. Ongoing research with biologics will provide new insights and further extend the promising scenario of their effects in asthma management.

Declaration of interest

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