



Controversies and opportunities in severe asthma

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Purpose of review

Despite currently available treatments, many asthma patients remain inadequately controlled, but identifying distinct patient populations (phenotypes/endotypes) may optimize their management. This review discusses some of the controversies and opportunities for improved disease control in severe asthma.

Recent findings

Currently approved anti-immunoglobulin E and anti-interleukin 5 biologics, which target specific pathways instead of using a 'one size fits all' strategy, are efficacious and well tolerated therapies for severe asthma. The appropriate use of these biologics, and of those in development (e.g., benralizumab and dupilumab), should be aided by further understanding of asthma phenotypes and endotypes, utilizing appropriate biomarkers.

Oral corticosteroids are often added as maintenance therapy for patients with severe uncontrolled asthma, but their use is associated with significant adverse effects and should be considered a last option. The true cost of this therapy, including the cost of morbidities associated with its use, remains to be determined. Severe asthma in pediatrics poses a unique opportunity for possible prevention strategies and the potential for primary prevention. Although several avenues for primary prevention are being explored and are out of the scope of this review, we focus our discussion on the use of omalizumab, which has been recently explored in clinical trials.

Summary

Appropriate use of biologics in severe asthma should be supported by further understanding of biomarkers predicting response to targeted therapy. Because of their association with significant adverse effects, add-on oral corticosteroids should be considered a last treatment option for patients with uncontrolled severe asthma. Finally, severe asthma in pediatrics poses a unique opportunity for potential prevention strategies.

Keywords

anti-immunoglobulin E, anti-interleukin 5, asthma, biologics, biomarker, endotype, oral corticosteroid, pediatric asthma, phenotype, severe asthma

INTRODUCTION

The current goals of asthma therapy are asthma control and reduction of future risks [1[¶],2]. Asthma management aims at reducing symptoms and exacerbations, improving lung function and quality of life (QoL), and reducing long-term side-effects of therapies [1[¶],2]. To standardize asthma treatment, the Global Initiative for Asthma strategy uses five distinct steps for therapy: Steps 1–3 focus on the use of low-dose inhaled corticosteroids (ICS), which are supplemented with additional controller medications, followed by the addition of long-acting β -2-agonists as the severity increases; those patients who fail to respond to Step 3 treatment options are considered to have severe asthma and are escalated to Step 4, and, if necessary, to Step 5 (reviewed in the following section) [2].

Despite currently available therapies, many asthma patients remain inadequately controlled

[3] and their disease negatively impacts productivity and QoL [4,5]. Long-term ICS treatment in both children and adults does not achieve remission of asthma and reports on the effect of ICS on loss of lung function over time have been inconsistent [6–8].

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KEY POINTS

- The heterogeneity of asthma and the treatment response variability are major barriers to successful asthma management.
- Anti-IgE and anti-interleukin 5 biologics, which target specific molecular pathways of asthma, are efficacious and well tolerated treatment options for severe asthma.
- The appropriate use of biologics is likely to be supported by further understanding of asthma phenotypes and endotypes, utilizing appropriate biomarkers.
- Oral corticosteroids are associated with significant adverse effects and are considered a last option in current treatment strategy.
- Severe asthma in pediatrics poses a unique opportunity for potential prevention strategies.

Factors that contribute to poorly controlled asthma include incorrect inhaler technique, poor adherence, and major psychological or socioeconomic problems [1^{••}]. Moreover, the heterogeneity of asthma and the treatment response variability are major barriers to successful asthma management [3,9,10], but identifying distinct patient populations (phenotypes/endotypes) may optimize the management of patients with uncontrolled disease [11^{••},12[•]].

The review briefly discusses some of the controversies and opportunities for improved disease control in severe asthma.

POSITIONING OF BIOLOGICS: WHERE ARE WE AND WHERE DO WE GO FROM HERE?

Biologic therapies have the advantage of targeting specific molecular pathways of asthma, which may, as a consequence, increase efficacy and limit the potential complications associated with nonspecific

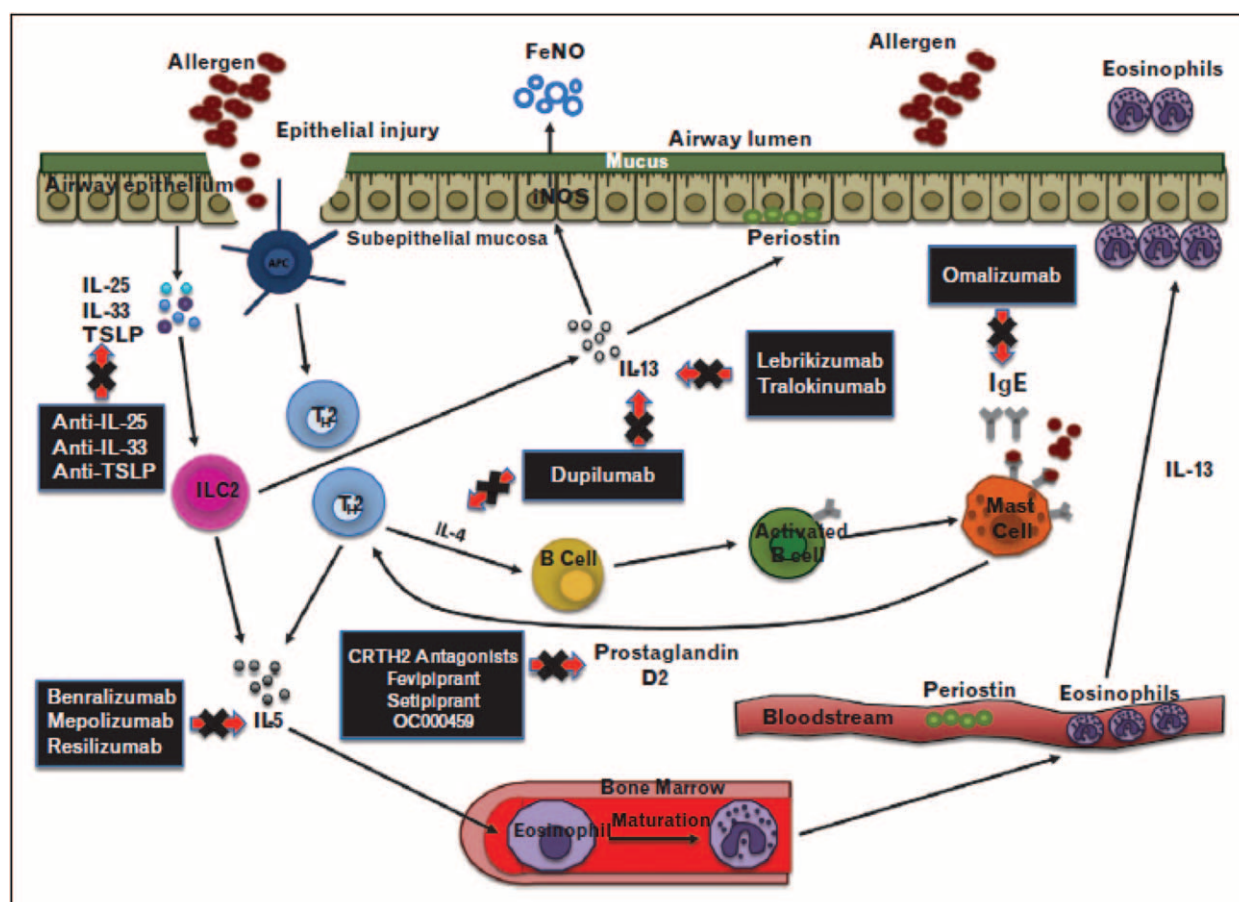


FIGURE 1. Targets of type 2 inflammation and biologic treatments. APC, antigen-presenting cell; CRTH2, chemoattractant receptor-homologous molecule expressed on TH2 cells; FeNO, fractional excretion of nitric oxide; IgE, immunoglobulin E; IL, interleukin; ILC2, type-2 innate lymphoid cells; iNOS, inducible nitric oxide synthase; TH2, T-helper type 2; TSLP, thymic stromal lymphopoietin. Reproduced with permission [14].

Table 1. Summary of biologics targeting type 2-high moderate-to-severe asthma

Biologic therapy	Mechanism of action	Potential biomarker	Summary of main findings ^a
Omalizumab (approved)	Blocks the interaction of IgE with FcεRI	Better treatment responses with higher FeNO values and blood eosinophil counts ≥ 260 cells/ μ L [17 [■] ,18] although recent real-life data indicate that efficacy may be similar in high (>300 cells/ μ L) and low (<300 cells/ μ L) blood eosinophil subgroups [19]	Systematic review and meta-analysis ($n=6382$; studies = 25, of which 3 focused exclusively on a pediatric or adolescent population) [20[■]] Patients with moderate or severe asthma randomized to receive omalizumab or placebo Asthma exacerbations (primary outcome measure): significant reduction in the odds of having ≥ 1 exacerbations in the steroid stable phases with omalizumab versus placebo (OR, 0.55; 95% CI, 0.42–0.60; $n=3261$; studies = 10) Absolute reduction from 26% for patients suffering an exacerbation on placebo to 16% on omalizumab, over 16–60 weeks Hospitalizations: significant benefit noted for omalizumab versus placebo (OR, 0.16; 95% CI, 0.06–0.42; $n=1824$; studies = 4; $P=0.00017$) Absolute reduction in risk from 3% with placebo to 0.5% with omalizumab, over 28–60 weeks Medication-sparing outcomes (primary outcome measure) Omalizumab-treated patients significantly more likely to be able to withdraw their ICS completely versus placebo-treated patients (OR, 2.50, 95% CI, 2.00–3.13; $P<0.00001$) A small but significant reduction in daily ICS dose reported for omalizumab-treated patients compared with those on placebo (weighted MD, -118.8 μg beclomethasone dipropionate equivalent/day, 95%CI, -154.4 to -83.1; $P<0.00001$) No significant difference between the two groups for the number of patients who were able to withdraw from OCS therapy Small but significant reduction in rescue β_2-agonist medication with omalizumab versus placebo (MD, -0.39 puffs/day, 95% CI, -0.55 to -0.24; $n=3524$; studies = 9) Asthma control In the steroid stable phase, global asthma control was significantly better when taking omalizumab than placebo (OR, 2.12; 95%CI, 1.67–2.68; $n=1136$; studies = 4; $P<0.00001$); significant advantage for omalizumab versus placebo observed in the moderate-to-severe (OR, 3.32; 95% CI, 2.19–5.05; $P<0.00001$) and in the severe (OR, 1.69; 95% CI, 1.26–2.26; $P=0.00047$) subgroups In the steroid reduction phase, moderate-to-severe patients were more likely to rate treatment as ‘good’ or ‘excellent’ when treated with omalizumab than with placebo (OR, 2.72; 95% CI, 2.04–3.62; $n=842$; studies = 2) Asthma-related QoL In the steroid stable phase, there was a significantly greater improvement from baseline in the overall AQLQ with omalizumab versus placebo (MD, 0.31, 95%CI, 0.23–0.39; $n=2981$; studies = 6); however, this finding did not reach the validated clinically relevant effect size of 0.5
Mepolizumab (approved)	IL-5 antagonist	Blood eosinophil count ≥ 150 cells/ μ L at treatment initiation or ≥ 300 cells/ μ L in past year [21 [■]]	Systematic review and meta-analysis ($n=1707$; studies = 8) [22[■]] Patients with severe eosinophilic asthma randomized to receive mepolizumab or placebo Mepolizumab led to improvements in health-related QoL and reductions in asthma exacerbation rates (primary outcome measures) Trend favoring IV mepolizumab versus placebo for AQLQ scores (MD, 0.21, 95% CI, -0.01 to 0.44; $n=682$, studies = 2; $P=0.058$) Significant difference between IV mepolizumab and placebo for SGRQ scores (MD, 6.40; 95% CI, 3.15–9.65; $n=576$; studies = 1; $P=0.00012$), indicating a clinically important benefit favoring mepolizumab Significant reduction in clinically significant exacerbation rates with IV mepolizumab versus placebo (RR, 0.52; 95% CI 0.43–0.64; $n=690$; studies = 2 (patients with eosinophilic asthma); $P<0.00001$) However, no significant difference between IV mepolizumab and placebo using a random-effects model (RR, 0.67; 95% CI, 0.34–1.31; $n=468$) in four studies not limited to eosinophilic asthma No significant increase with mepolizumab treatment versus placebo in measures of lung function (FEV₁ or PEFr) No significant difference between groups (250 mg or 750 mg IV mepolizumab and placebo) in asthma symptoms using an asthma symptom score or the JACQ Significant difference in asthma symptoms between 75 mg IV mepolizumab and placebo (MD, -0.30; 95% CI, -0.55 to -0.04; $n=690$; studies = 2; $P=0.021$) and between SC mepolizumab and placebo (MD, -0.44; 95% CI, -0.64 to -0.24; $n=385$; studies = 1)
Reslizumab (approved)	IL-5 antagonist	Blood eosinophil count ≥ 400 cells/ μ L [23 [■]]	Systematic review and meta-analysis ($n=1366$; studies = 5) [24] Patients with severe eosinophilic asthma randomized to receive reslizumab or placebo Reslizumab superior to placebo Asthma exacerbations (OR, 0.46; 95% CI, 0.35–0.59; $P<0.00001$) FEV₁ (standardized MD, 0.16; 95% CI, 0.10–0.23; $P<0.00001$) ACQ score (standardized MD, -0.26; 95% CI, -0.36 to -0.16; $P<0.00001$) Blood eosinophil counts (standardized MD, -475.62; 95% CI, -528.41 to -422.83; $P<0.00001$)

Table 1 (Continued)

Biologic therapy	Mechanism of action	Potential biomarker	Summary of main findings ^a
Benralizumab (in development)	IL-5R antagonist; targets eosinophils and basophils	Blood eosinophil count ≥ 300 cells/ μ L [25 [■]] but a recent analysis has shown improvements in patients with blood eosinophil counts ≥ 150 cells/ μ L [26]	CALIMA [27 [■]] and SIROCCO [25 [■]] Compared with placebo, benralizumab reduced the annual asthma exacerbation rate over 56 [27 [■]] or 48 [25 [■]] weeks when given every 4 weeks (RR, 0.64; 95% CI 0.49–0.85; $P=0.0018$; [27 [■]] RR 0.55; 95% CI 0.42–0.71; $P<0.0001$; [25 [■]]) or every 8 weeks (RR, 0.72; 95% CI 0.54–0.95; $P=0.0188$; [27 [■]] RR, 0.49; 95% CI, 0.37–0.64; $P<0.0001$ [25 [■]]) Both benralizumab dosing regimens also significantly improved prebronchodilator FEV ₁ at weeks 56 [27 [■]] or 48 [25 [■]] Total asthma symptom score at weeks 56 [27 [■]] or 48 [25 [■]] was significantly improved by the every 8 weeks regimen only ZONDA [28 [■]] Benralizumab every 4 or 8 weeks significantly reduced the median final OCS doses from baseline by 75% versus a reduction of 25% in the placebo group ($P<0.001$, in both cases) The odds of a reduction in the OCS dose were >4 times as high with benralizumab as with placebo Benralizumab also resulted in an annual exacerbation rate that was 55% lower (every 4 weeks; marginal rate, 0.83 versus 1.83; $P=0.003$) or 70% lower (every 8 weeks; marginal rate, 0.54 versus 1.83; $P<0.001$) than the rate with placebo At 28 weeks, there was no significant effect of either benralizumab regimen on FEV ₁ versus placebo
Tralokinumab (in development)	IL-13 antagonist	Increased blood periostin and DPP-4 levels [29]	At week 52, % changes in annual asthma exacerbation rate were not significant with tralokinumab every 2 weeks or every 4 weeks versus placebo [6% (95% CI, –31 to 33; NS) and –2% (–46 to 29; NS)], respectively [29] Prebronchodilator FEV ₁ was significantly increased with tralokinumab every 2 weeks versus placebo (change from baseline 7.3% (95% CI, 2.6–12.0); $P=0.003$), but not with tralokinumab every 4 weeks [1.8% (–2.9 to 6.6); NS] [29]
Lebrikizumab (development terminated)	IL-13 antagonist	Increased blood periostin and blood eosinophils [30]	A pooled analysis [30] of the phase 2b studies LUTE and VERSE showed that treatment with lebrikizumab reduced the rate of asthma exacerbations and was associated with improved lung function However, variable results were reported in two phase 3 RCTs (LAVOLTA I and II) for the primary endpoint of a significant reduction in the rate of asthma exacerbations over 52 weeks, which led to the termination of the clinical program in asthma [31]
Dupilumab (in development)	IL-4R antagonist; inhibits IL-13 and IL-4	Better responses with blood eosinophil count ≥ 300 cells/ μ L, although improvements observed in all patients, irrespective of baseline eosinophil count [32 [■]]	The greatest increases in FEV ₁ versus placebo [0.18 l (SE, 0.05)] were observed at week 12 with doses every 2 weeks in the 300 mg group [mean change, 0.39 l (SE, 0.05); MD, 0.21 (95% CI, 0.06–0.36, $P=0.0063$)] and in the 200 mg group [mean change, 0.43 l (SE, 0.05); MD, 0.26 (0.11–0.40, $P=0.0008$)] in the subgroup with baseline blood eosinophil count ≥ 300 cells/ μ L [32 [■]] Similarly, dupilumab every 2 weeks produced the greatest reductions in annualized rates of exacerbation in the subgroup with ≥ 300 eosinophils/ μ L (71.2–80.7%) [32 [■]]

^aWhere available, findings from systematic reviews and meta-analyses are reported.

ACQ, Asthma Control Questionnaire; AQLQ, Asthma Quality of Life Questionnaire; CALIMA, A Multicentre, Randomized, Double-blind, Parallel Group, Placebo-controlled, Phase 3 Study to Evaluate the Efficacy and Safety of Benralizumab in Asthmatic Adults and Adolescents Inadequately Controlled on Inhaled Corticosteroid Plus Long-acting β_2 Agonist; CI, confidence interval; DPP-4, dipeptidyl peptidase-4; Fc ϵ RI, high-affinity IgE receptor; FeNO, fractional exhaled nitric oxide; FEV₁, forced expiratory flow in one second; IgE, immunoglobulin E; IL, IV, intravenous; JACQ, Juniper Asthma Cough Questionnaire; LAVOLTA, A Phase III, Randomized, Double-Blind, Placebo-Controlled Study to Assess the Efficacy and Safety of Lebrikizumab in Patients With Uncontrolled Asthma Who Are on Inhaled Corticosteroids and a Second Controller Medication; LUTE, A Phase III, Randomized, Double-Blind, Placebo-Controlled Study to Assess the Safety and Efficacy of Lebrikizumab in Patients With Uncontrolled Asthma Who Are on Inhaled Corticosteroids and a Second Controller Medication; MD, mean difference; NS, not significant; OR, odds ratio; PEFR, peak expiratory flow rate; RCT, randomized controlled trial; SC, subcutaneous, SE, standard error; SGRQ, St George's Respiratory Questionnaire; SIROCCO, A Multicentre, Randomized, Double-blind, Parallel Group, Placebo-controlled, Phase III Efficacy and Safety Study of Benralizumab (MEDI-563) Added to High-dose Inhaled Corticosteroid Plus Long-acting β_2 Agonist in Patients With Uncontrolled Asthma; VERSE, A Phase III, Randomized, Double-Blind, Placebo-Controlled Study to Assess the Efficacy and Safety of Lebrikizumab in Patients With Uncontrolled Asthma Who Are on Inhaled Corticosteroids and a Second Controller Medication; ZONDA, A Multicenter, Randomized, Double-blind, Parallel Group, Placebo-controlled, Phase 3 Efficacy and Safety Study of Benralizumab (MEDI-563) to Reduce Oral Corticosteroid Use in Patients With Uncontrolled Asthma on High Dose Inhaled Corticosteroid Plus Long-acting β_2 Agonist and Chronic Oral Corticosteroid Therapy.

effects of more traditional treatments [13,14]. Most biologics currently approved or those late in development target type 2-high asthma [mainly directed at immunoglobulin E (IgE), interleukin 4, interleukin 5, and interleukin 13] [14–16] (Fig. 1 and Table 1). Table 1 summarizes recent main findings with the agents included in this review. In addition to the biologics included here, several others, directed at targets such as thymic stromal lymphopoietin, prostaglandin D2 receptor, interleukin 25

and interleukin 33, are currently in various stages of development [14].

Currently approved biologics

Anti-immunoglobulin E

IgE plays a key upstream role in the inflammatory cascade underlying allergy and allergic asthma [33] and it is estimated that more than half of patients

with poorly controlled asthma have allergic IgE-mediated asthma and therefore may respond to treatments targeting IgE [34].

Omalizumab, the first mAb used in asthma therapy, was approved in 2003 and to date has accumulated more than 500 000 patients treated worldwide [35–37]. This agent has demonstrated efficacy and safety in numerous clinical and real-life studies of adult and pediatric patients with moderate-to-severe allergic asthma [17[■],20[■],37–44]. The benefits of omalizumab, as reported in clinical trials, include a reduction in exacerbation rates, fewer emergency department visits, ICS dose reduction, improvement in asthma symptom control, and better asthma-related QoL. In addition, the effectiveness of omalizumab has been investigated in real-life studies, which have corroborated and extended clinical findings [41,44–47].

A post-hoc analysis of biomarkers (fractional exhaled nitric oxide, blood eosinophils, and serum periostin) in the omalizumab A Phase IIIb Multicenter, Randomized, Double-Blind, Placebo-Controlled Study of Xolair in Subjects With Moderate to Severe Persistent Asthma Who Are Inadequately Controlled With High-Dose Inhaled Corticosteroids and Long-Acting Beta-Agonists (EXTRA) study revealed that the treatment effect of omalizumab (% reduction in exacerbations) was greater in all three high baseline biomarker subgroups versus the low biomarker subgroups, indicating that these patients may achieve greater benefit from omalizumab therapy [17[■]]. Furthermore, patients with eosinophil counts at least 300 cells/ μ l showed a better response to omalizumab, with up to a 60% decrease in asthma exacerbations [18]. However, a recent large real-life study has suggested that omalizumab may be effective in both high (≥ 300 cells/ μ l) and low eosinophil (< 300 cells/ μ l) severe allergic asthma patient subgroups [19].

Some studies have suggested that some nonatopic asthmatic patients may also benefit from omalizumab therapy, but there is a need for further investigation to more fully assess its clinical efficacy in this setting, as well as to identify predictors of response to treatment [48–51].

Anti-interleukin 5 agents

Eosinophils and their mediators are key effectors of severe eosinophilic asthma [52] and interleukin 5 is a proeosinophilic type 2 cytokine, which binds to the interleukin 5 receptor α expressed on eosinophils and basophils; it promotes eosinophil differentiation, survival, and activation [15,34,53] and contributes to airway eosinophilic inflammation [15].

Mepolizumab and reslizumab have been approved for maintenance treatment of severe eosinophilic asthma [22[■],37,40,54]; both have been shown to reduce asthma exacerbations and improve asthma-related QoL and lung function [22[■],40,54]. Also, both agents have been reported to be generally well tolerated, with overall safety profiles comparable with placebo [22[■],37,40,54].

Baseline blood eosinophil counts have been shown to predict treatment response with these agents, with decreased asthma exacerbations and improvement in forced expiratory volume in 1 s (FEV₁) being observed in patients with blood eosinophil count at least 150 cells/ μ l at treatment initiation or at least 300 cells/ μ l in the past year (mepolizumab) or at least 400 cells/ μ l (reslizumab) [21[■],23[■],55]. Moreover, in patients requiring daily oral corticosteroid (OCS) to maintain asthma control, mepolizumab demonstrated a significant OCS-sparing effect [56[■]].

Biologics in development

Anti-interleukin 5 receptor: benralizumab

Two phase 3 randomized controlled trials demonstrated that benralizumab significantly reduced asthma exacerbations and improved prebronchodilator FEV₁ in patients with severe, uncontrolled asthma with eosinophilia (blood eosinophil counts ≥ 300 cells/ μ l) [25[■],27[■]]. Most recently, a phase 3 trial found that benralizumab significantly reduced median final OCS doses from baseline by 75%, compared with a reduction of 25% in the placebo group; clinically relevant benefits were also observed on exacerbation rates, but there was no effect on FEV₁ at 28 weeks [28[■]].

Anti-interleukin 13 and anti-interleukin 4 agents

Interleukin 13 and interleukin 4 are involved in IgE synthesis, eosinophil activation, mucus secretion, and airway remodeling [15,57]. Interleukin 13 is essential to the development of airway hyperresponsiveness in asthma, and its effect is facilitated through the low-affinity interleukin 13 receptor $\alpha 1$ (IL 13R $\alpha 1$) and IL 4R α complexes (IL 13R $\alpha 1$ /IL 4R α complex) [15,58,59]. The effect of interleukin 4 is also mediated through IL 4R α [15,59]. With the exception of lebrikizumab, which has recently had its clinical program in asthma terminated, all agents targeting these pathways are still in development.

A phase 2b randomized controlled trial of tralokinumab (an interleukin 13 antagonist) found improvements in FEV₁ in patients receiving the

treatment every 2 weeks, but not in those receiving it every 4 weeks and the primary endpoint of annual asthma exacerbation rates at week 52 was not significantly different from placebo [29]. Furthermore, it was recently announced that in a phase 3 trial, tralokinumab failed to meet its primary endpoint of a significant reduction in the annual asthma exacerbation rate at week 52 versus placebo [60]. For similar reasons of inconsistent demonstrated efficacy, another interleukin 13 antagonist, lebrikizumab, is no longer in clinical development (see Table 1 for details).

The IL 4R blocker dupilumab (inhibits both interleukin 4 and interleukin 13 signaling) has shown promising results, suggesting that there may be advantages to suppressing the activity of both interleukin 4 and interleukin 13 [15]. Specifically, a phase 2b dose-ranging study showed that add-on treatment with dupilumab significantly improved lung function and reduced the rate of severe exacerbations; there were also significant improvements in patient-reported outcomes, such as asthma-related QoL and asthma symptom scores at week 24 [32[■]]. The favorable effects were noted irrespective of baseline blood eosinophil count [32[■]]. Dupilumab is now approved in the United States for the treatment of adults with moderate-to-severe atopic dermatitis and has more recently also received a positive opinion for use for this condition in the European Union.

Therapies for type 2-low asthma

Importantly, around 40% of patients with severe asthma do not have type 2 inflammation [61] and type 2-low asthma patients respond poorly to both currently approved biologics and corticosteroids [10,15,36,55]. Investigational approaches in type 2-low asthma targeted the interleukin 17 receptor in moderate-to-severe asthma, but the anti-interleukin 17 agent brodalumab did not show any treatment differences compared with placebo [62], and a follow-up phase 2b study in the high-reversibility subgroup (postbronchodilator FEV₁ improvement $\geq 20\%$) was stopped because of lack of efficacy [63]. Hence, treatment options for type 2-low asthma remain an unmet need [14].

Current treatment strategy: where do biologics fit in?

Current asthma treatment strategy [2] indicates the use of omalizumab for the treatment of moderate or severe allergic asthma in patients at least 6 years of age and mepolizumab or reslizumab for severe eosinophilic asthma in patients at least 12 years of

age, before chronic treatment with OCS is initiated (Step 5). There is good evidence (Grade A) for add-on treatment with omalizumab for patients at least 6 years of age with moderate or severe allergic asthma that is uncontrolled on Step 4 treatment (≥ 2 controllers and as-needed reliever medication) [20[■],43] and Grade B evidence for add-on treatment with anti-interleukin 5 (subcutaneous mepolizumab; intravenous reslizumab) for patients at least 12 years of age with severe eosinophilic asthma that is uncontrolled on Step 4 treatment [23[■],64,65]. Add-on OCS is the last treatment option for patients with uncontrolled severe asthma [2].

With regards to conditions for stopping treatment with biologics, the omalizumab European label specifies that this agent is for long-term use, but that at 16 weeks after commencing omalizumab treatment, patients should be assessed by their physician for treatment efficacy before further injections are administered [66]. For mepolizumab, the National Institute for Health and Clinical Excellence in the United Kingdom recommends stopping mepolizumab at 12 months of treatment if the asthma has not responded adequately or continuing treatment if the asthma has responded adequately and assessing continued responsiveness each year [67]. A proposal for a 'traffic-light system' for response and nonresponse following at least 4 months of treatment with an antieosinophilic therapy has recently been put forward by a European expert task force of clinicians [12[■]].

Finally, it would be useful to determine the first choice of treatment for new cases of severe asthma and also when to switch from one mAb to another. In the absence of any studies directly comparing anti-IgE and anti-interleukin 5 treatments, it is currently impossible to prioritize a first-line biologic.

PHENOTYPES AND ENDOTYPES

The understanding and applicability of biologic therapy in severe asthma remains to be elucidated, as further research (especially head-to-head trials) is required to determine specific populations that will benefit the most from a particular biologic agent – one treatment does not fit all, hence the need for a personalized or precise approach to management [3,35,68]. Froidure *et al.* [69[■]] have recently proposed a decision chart, which is based on the current knowledge of efficacy of add-on treatments in the most prevalent phenotypes (observable disease characteristics) and endotypes (distinct pathophysiological mechanisms) of severe asthma (Fig. 2).

Appropriate use of biologics is also likely to be supported by further understanding of biomarkers [35,68,70], although currently these are not

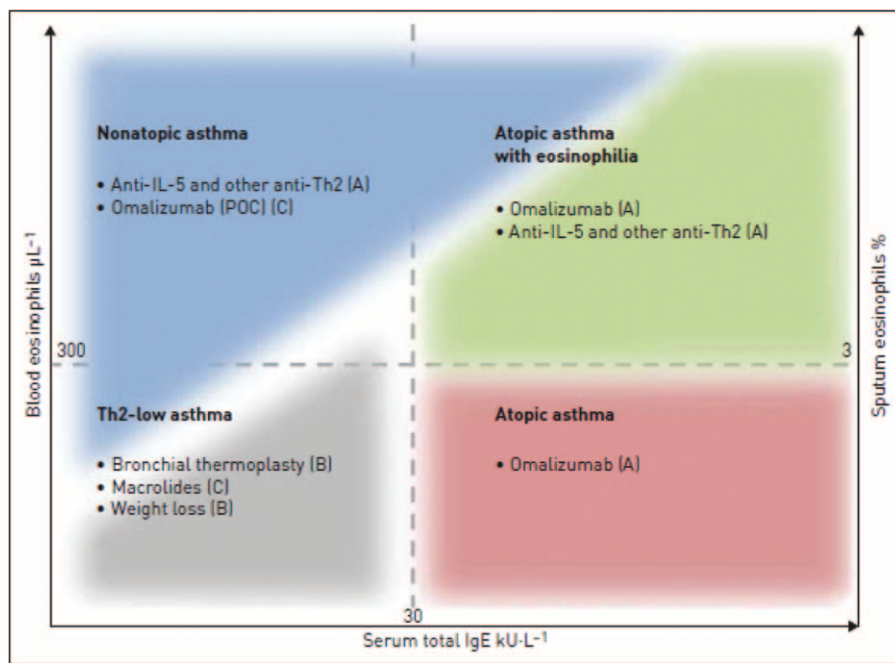


FIGURE 2. Decision chart based on the current knowledge of efficacy of add-on treatments in the most prevalent phenotypes and endotypes of severe asthma. A, B, and C correspond to the available levels of evidence. IgE, immunoglobulin E; IL, interleukin; POC, proof of concept; Th, T-helper. Reproduced with permission [69].

sufficiently precise to select the endotype that specifically responds to a targeted therapy [71].

The high heterogeneity of severe asthma likely contributes to the interindividual variability in treatment response [3,72,73] and being able to phenotype and endotype patients permits a more rational approach to selecting a specific biologic agent for a specific patient [55]. This will enable the provision of true personalized medicine and, subsequently, more efficient use of healthcare resources [74]. Phenotyping and endotyping is especially pertinent in childhood asthma, as this is the key period that is amenable to potential prevention strategies [74].

Biomarkers can help define phenotypes and endotypes, although most biomarkers that have been described in asthma are not commonly available or still require external validation [70].

IMPACT OF CHRONIC ORAL CORTICOSTEROID USE

When standard therapies fail to provide adequate control of severe asthma, OCS is often added as maintenance therapy [75]. However, OCS use has been associated with dose and duration-dependent serious adverse effects, such as osteoporosis, diabetes mellitus, infections, hypertension, cataracts, weight gain, Cushingoid features, adrenal suppression, and psychiatric disturbances [76–78].

A real-life study of omalizumab in uncontrolled persistent allergic asthma (The eXpErience Registry) found that 28.6% of patients were taking maintenance OCS at baseline [79]. However, the optimal timing for initiation of OCS therapy has not been identified and it is unclear whether continuous low-dose OCS treatment is better than multiple intermittent bursts for controlling exacerbations [75]. A recent study [80] investigating the association between OCS and adverse effects based on the number of OCS prescriptions found that the number of prescriptions dispensed within a year was strongly associated with adverse effects, irrespective of dose and duration. Thus, it appears that the use of OCS bursts is harmful to the patient, especially if at least four prescriptions/year are required [80]. Another recent study [81], which evaluated the patient characteristics and disease burden associated with chronic OCS use by adults with persistent asthma, found that baseline factors which were significantly associated with chronic OCS use in the follow-up year included demographic characteristics, disease burden, greater blood eosinophil counts and, most strongly, chronic OCS use [81].

OCS drug acquisition costs are very low, as they are available in generic formulations [76,80], but the trade-off for their use to achieve asthma control and manage exacerbations includes adverse effects, which ultimately may result in a poor QoL and increased healthcare resource use and costs

[76,82]. Hence, it is important to limit the use of OCS and consider alternative treatments for severe or refractory asthma [76]. As already discussed, biologics are efficacious and OCS-sparing effects have been observed with omalizumab [79,83,84], mepolizumab [56], and benralizumab [28]. Further studies are needed to evaluate the true cost of OCS therapy, including the cost of morbidities associated with its use, and how this compares with the overall cost of treatment alternatives [80].

SEVERE ASTHMA IN PEDIATRICS

Although control of asthma can be achieved in many children by using conventional therapies (assuming adherence) and/or by avoiding triggering factors, 3–5% of pediatric patients do not respond to standard treatment and are known as having uncontrolled severe persistent asthma [38,85].

Most studies of asthma therapies have been conducted in adults; hence, there is currently a need for research in children with severe asthma [85,86]. Conventional bronchodilator and anti-inflammatory treatments do not modify the underlying disease mechanism; also, the safety of prolonged high-dose ICS use and the safe and appropriate use of long-acting β -2-agonists in children have been debatable [38,87–89]. ICS therapy has been shown to affect growth velocity in prepubertal children in the first 1–2 years of treatment, although the study which investigated long-term outcomes [90] showed a difference of only 0.7% in adult height [2,91] and the final height achievement appears to depend on the type of corticosteroid, duration of treatment, and cumulative dose [92]. Similarly to observations in adults, long-term treatment with OCS is associated with toxicity in children, with the most common adverse effects being weight gain, Cushingoid features, growth retardation, and increased susceptibility to infections [78].

In contrast, evidence from both clinical and real-life studies suggests that omalizumab, which has more than 7 years of approved use in Europe in pediatric patients, can help address the important unmet need in children with a high disease burden [38]. Further large, long-term studies, and continued monitoring will help elucidate the impact of omalizumab therapy on the natural history of severe childhood asthma [38,93]. Also, the criteria and the timing for discontinuing omalizumab need to be defined. The findings of one small, uncontrolled study, which involved a 4-year follow-up of children with moderate-to-severe uncontrolled allergic asthma after withdrawal of 1-year omalizumab treatment, raise the possibility that omalizumab may potentially have disease-modifying activity [94].

Previous studies in adults have shown positive effects of omalizumab in reducing airway inflammation and remodeling [95–97].

For school-aged children, asthma exacerbations predictably occur in the fall, when they return to school. To determine if the administration of omalizumab to at-risk children right before they return to school could prevent these predictable exacerbations, the Preventive Omalizumab or Step-up Therapy for Fall Exacerbations study was undertaken to investigate whether adding omalizumab 4–6 weeks before return to school to ongoing guidelines-based management among innercity asthmatic children (aged 6–17 years; ≥ 1 recent exacerbations), reduces fall asthma exacerbations in patients with severe disease, and especially in those with a recent exacerbation, irrespective of disease severity [98]. The fall exacerbation rate was significantly lower in the omalizumab arm versus the placebo arm (guideline-directed care), particularly among patients with an exacerbation during the run-in phase. The effects of omalizumab on interferon- α generation to rhinovirus during an in-vitro incubation with peripheral blood mononuclear cells were examined in a subset of patients and within the omalizumab group; those patients with greater increases in interferon- α generation were associated with fewer exacerbations (odds ratio, 0.14; 95% confidence interval, 0.01–0.88) [98]. Finally, in the Preventive Omalizumab or Step-up Therapy for Fall Exacerbation study, treatment with omalizumab decreased the duration of rhinovirus infections, viral shedding, and the risk of a rhinovirus illness, thus providing direct evidence that, by blocking IgE, it is possible to decrease susceptibility to rhinovirus infections and subsequent illness [99].

The Controlling and Preventing Asthma Progression and Severity in Kids (CASK) study (NCT02570984) is currently being planned, to investigate whether 2 years of omalizumab treatment in preschool children at high risk for asthma will prevent the progression to childhood asthma.

CONCLUSION

The management of severe asthma is challenging because of the heterogeneity of the disease pathophysiology and response to therapy. Currently approved biologics for severe asthma (omalizumab, mepolizumab, and reslizumab) have all shown beneficial treatment effects in specific populations when added to standard therapy and results with benralizumab and dupilumab are promising. Appropriate use of these, and future, biologics is likely to be supported by further understanding of asthma phenotypes and endotypes and the utility of

existing and emerging biomarkers, so that the most suitable biologic is selected for the appropriate patient. Although OCS treatment is often added as maintenance therapy in severe uncontrolled asthma patients, its use is associated with serious adverse effects and should be considered a last option. Finally, severe asthma in pediatrics represents a unique opportunity for possible prevention strategies and the potential for primary prevention with omalizumab has been recently explored.

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Conflicts of interest

M.H. has relationships with drug companies, including AstraZeneca, GSK, Merck, Novartis, Roche, Sanofi/Regeneron and TEVA. In addition to being investigator in trials involving these companies, relationships include consultancy service and membership of scientific advisory boards.

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- of special interest
- of outstanding interest

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