



Biologic agents for severe asthma patients: clinical perspectives and implications

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Abstract

Asthma is a chronic inflammatory multifactorial disorder of the airways characterized by the involvement of immune cells and mediators in its onset and maintenance. Traditional therapeutic strategies have been unsatisfactory in controlling the underlying pathology, especially in the more severe states. Hence in the last couple of decades, new biological approaches targeting molecular mediators have been developed. In this narrative review we examine biological agents currently available for the management of severe asthma, focusing our attention on their clinical application, pros and cons, and in particular on gaps regarding the use of these agents. The most well-known and used biologic agent in clinical practice is omalizumab, though there is emerging evidence for mepolizumab too. The future of these biological therapies is to broaden our knowledge of their practical use and ascertain predictive biomarkers, or define an algorithm, useful in the optimal application of these ‘biological weapons’.

Keywords Severe asthma · Biologic drugs · Anti-IgE · Anti-IL-5 · Omalizumab · Mepolizumab

Abbreviations

AQLQ	Asthma Quality of Life Questionnaire
ACQ	Asthma Control Questionnaire
BHR	Bronchial hyper-responsiveness
DBPC	Double blind placebo controlled
EMA	European Medicine Agency
FDA	Food and Drug Administration
FEV ₁	Forced expiratory volume in the 1st second
GETE	Global evaluation of treatment effectiveness
ICS	Inhaled corticosteroids
LABA	Long-acting b2-adrenoceptor agonists
mAb	Monoclonal antibody
OCS	Oral corticosteroids

QoL	Quality of life
RCTs	Randomized controlled trials
SGRQ	St. George’s Respiratory Questionnaire

Introduction

Asthma is a chronic inflammatory disorder of the airways characterized by mast cells and respiratory tract granulocytes infiltration/activation, driven by specific cytokines and chemokines produced by CD4⁺ lymphocytes. The chronic inflammation is associated with progressive remodeling of the airway tissues and bronchial hyper-responsiveness (BHR) that leads to the clinical manifestations of the disease: recurrent episodes of wheezing, breathlessness, chest tightness and coughing [1, 2].

Th2 inflammation is present in approximately 50% of mild to moderate asthma and probably in a higher proportion of severe asthma patients [3]. However, the commonly accepted paradigm that Th2 phenotype and, consequently, IgE over-production and eosinophilia are central to the pathogenesis of severe asthma [4, 5] has been recently challenged with emerging alternative T cell subtypes (e.g., Th1 cells, regulatory T cells and Th17 cells) [6–8] and other mediators playing a more prominent role [9–11] and contributing to a wide array of assorted endotypes [12, 13].

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Thus, such a complex multi-factorial disease would require a diverse management strategy capable of simultaneously addressing these clinical challenges.

Current clinical guidelines for asthma suggest that first-line therapy includes inhaled corticosteroids (ICS), and subsequently together with long-acting β_2 -adrenoceptor agonists (LABAs), or, alternatively, leukotriene receptor antagonists [14]. However, this therapeutic approach is often inadequate for the most severe forms of the disease and, therefore, it is necessary to add-on therapy (e.g. oral corticosteroids and tiotropium) [15] until improved disease control is attained. Sometimes these simple measures are sufficient to achieve good disease control and clinical remission, but in a minority of challenging patients, troublesome symptoms may re-emerge upon withdrawal of systemic corticosteroids, or persist despite high doses of these drugs. Moreover, the side effects of systemic corticosteroids are a reason for further concern. For these poorly responsive patients, more effective strategies need to be adopted.

In an attempt to address these unmet needs, a few biological agents intended to disable specific key inflammatory pathways associated with severe asthma have been approved and added to clinical guidelines; though this has only partially resolved the issue. As mentioned earlier, the well understood form of asthma is the Th2-driven phenotype, with high level of IgE and a marked atopic background; hence, the obvious target of the first biologic agent for use in severe asthma was directed at reducing circulating IgE, by means of the humanized IgG1 monoclonal antibody (mAb) anti-IgE, omalizumab. The Food and Drug Administration (FDA) approved omalizumab in 2003. Since then a number of new biologics have entered clinical development as anti-asthma therapies directed against various inflammatory targets (anti-CD4, anti-CD25, anti-OX40L, anti-interleukin (IL)-4, anti-IL-13, anti-IL-5, anti-IL-33, anti-IL-17 and anti-IL-25), but only one has been used as a long-term treatment in clinical practice, to-date.

Recently selective, orally active, DP2 receptor antagonists (at least 15 different molecules) and a selective DP1 receptor antagonist (Asapiprant) have been investigated for the treatment of asthma or allergic rhinitis. Although not biological agents, they deserve mention as an emerging therapeutic class due to the pathophysiological role of prostaglandin D_2 (PGD₂) in asthma; exerted by its interaction with the receptors DP1 and DP2 expressed on various cell types. DP1/DP2 receptor antagonists are generally safe and well tolerated. DP2 receptor antagonists have been proven to be effective in phase II proof-of-concept studies in adults with asthma either as monotherapy or as add-on therapy to ICS or montelukast. Treatment with some DP2 receptor antagonist for 4–12 weeks improved FEV1 in adults with asthma of different severity, compared to placebo. Importantly, the improvements were more pronounced in asthmatics with a

TH2-eosinophilic phenotype, particularly in patients with more severe airflow limitation [16].

In this narrative review, we will examine the biologics available for severe asthma treatment, with a focus on their application, defined as the clinical practice, beyond the clinical trials experience and out of the model of the experimental setting. With this in mind, we will focus our paper, on advantages and disadvantages of biologics, and in particular on the aspects that are still ongoing regarding their use, despite the positive results obtained so far. Furthermore, we will look at biologic drugs recently approved for use in severe asthma and those that are in the process of being approved, which may be available for clinical use in the near future.

Search method

In this review, we (MC, RE and MA) searched the PubMed and Scopus electronic database individually using keywords related to “severe asthma”, “biologics” (detailing in turn: anti-IgE, Anti-IL5, Anti-IL5R, Omalizumab, Mepolizumab, Reslizumab) with or without “real-life,” “clinical practice” and “long-term” by different combinations, and selecting case reports, clinical studies, clinical trials, controlled clinical trials, multicenter studies, observational studies and randomized controlled trials (RCTs). We then selected only studies that were judged relevant to the use of biologics in asthma in a real-life setting. Reference lists from these studies were also examined to identify significant articles. Additional information in abstracts presented at scientific congresses (in respiratory, immunology and allergy) available online were also included. In total 57 studies were identified as relevant the search criteria by author consensus.

Biologics in clinical practice

Three biological agents are currently available in clinical practice specifically indicated for the treatment of severe asthma: the anti-IgE, omalizumab (Xolair®, Novartis, Switzerland) and the anti-IL-5 mAbs, mepolizumab (Nucala®, GlaxoSmithKline, UK) and reslizumab (Cinqair®, Teva, Israel). In this section, we discuss the results obtained with these biologics and look quickly at their family of molecules currently under development.

Anti-IgE

The IgE signaling transduction pathway is one of the most investigated for the development of new drugs due to their key role in the activation of allergic cascade, which

underlies the pathophysiology in a reasonable proportion of asthmatics.

Omalizumab

Omalizumab is a recombinant humanized IgG1 monoclonal antibody that, binds free IgE, hence reducing their interaction with FCεRI receptors [17]. Furthermore, it is responsible for down regulation of these receptors on mast cells and basophils, with consequent reduction of cellular responses to allergens [18]. Omalizumab rapidly attenuates serum free IgE levels, preventing their interaction not only with FCεRI but with CD23 (FcεRII), too [19]. Consequently, omalizumab seems to induce B-cell anergy thereby decreasing IgE synthesis [20]. The mechanism of action of omalizumab in the treatment of asthma is believed to be multifactorial, and includes effects mediated through altered production of redox metabolites, vascular endothelial growth factor (VEGF) system, extrinsic coagulation pathway, oxidative markers related to miRNA, tumor necrosis factor-related apoptosis-inducing ligand (TRAIL)-related miRNA, and regulation in the production of known inflammatory proteins [21].

Omalizumab is administered by subcutaneous injection every 2 or 4 weeks; the dose is calculated based on body weight and serum IgE levels prior to treatment initiation. Its efficacy in severe allergic asthma is indisputably demonstrated in several clinical trials [22–30] (Table 1) and observational studies [31–39] (Table 2).

The INNOVATE study, compares the efficacy and safety of omalizumab vs placebo in a double-blind, placebo-controlled (DBPC) fashion in 419 difficult-to-treat asthmatic patients uncontrolled on high dose of LABA/ICS. The primary objective of the study is to evaluate the effect of add-on omalizumab on asthma exacerbations in patients with severe persistent asthma who were inadequately controlled despite GINA step 4 therapy. Omalizumab halves the severe exacerbation rate, and improves quality of life (QoL), lung function and symptoms scores with comparable adverse events to placebo [22]. The main limitation of this study is the 52-week period of treatment and observation, hence more recent studies have been performed with longer periods of observation with similar positive results in both adults and children [23, 31]. Moreover, a systematic review that selected only RCTs with the duration of treatment longer than 52 weeks, with a total of 2749 patients with persistent uncontrolled allergic asthma, confirms reduction in ICS use, improvement in Global Evaluation of Treatment Effectiveness (GETE) and Asthma-related QoL Questionnaire (AQLQ) scores in the omalizumab treated subjects. Additionally, omalizumab is well tolerated and cost-effective. Moreover, there is a significant reduction in exacerbation rates despite the heterogeneity in the definition of exacerbation influencing the results [29].

Asthmatic patients have very heterogeneous phenotypes and the population enrolled in trials is strictly selected so people with comorbidities, or specific characteristics regarding age, pulmonary function, etc. are often not eligible to be enrolled; only a percentage between 0 and 36%, but in most cases $\leq 10\%$, are enrolled [40]. Consequently, results obtained from clinical trials may differ substantially from the conditions that physicians have to treat in daily real-life situations, highlighting the limited value of RCTs. However, Gibson et al., from the Australian registry, have shown improvement of symptoms and reduction of OCS use in severe asthma patients with high prevalence of comorbidities with omalizumab use [41].

Omalizumab was introduced by the FDA in 2003 and by European Medicine Agency (EMA) in 2005 [17] as add-on therapy for severe allergic asthma with positive skin prick test or specific IgE to perennial allergens. Hence following more than 10 years of marketing, several studies in the real-life clinical setting have been published (Table 3) confirming and reinforcing the initial trial results albeit with their limitations of small cohorts or brief periods of observation [42–46].

More recent real-life studies have been included in a systematic review [47]. The authors list 24 studies with a total of 4117 severe asthmatic patients from 32 Countries in which omalizumab was administered show significant improvements in FEV1, severe exacerbation rates and subjective symptoms (GETE, ACQ, AQLQ). Additionally, healthcare resource utilization is reduced with medication sparing benefits as well as good safety profile data in the short- and long-term. All assessed parameters improve significantly after 16 weeks of treatment. This is the time frame to assess therapeutic response; i.e. in most cases after 16 weeks of treatment, patients can be divided in ‘responders’ and ‘non-responders.’

A review of 7 RCTs and 18 real-life studies using omalizumab in severe asthma patients, reaffirms the efficacy of omalizumab in terms of clinically related outcomes [48]. Despite several differences due to the two different approaches, in particular the heterogeneity of population, pre-treatment therapy and follow-up periods, the data reveal the same trend of benefits with a reduction in the number of exacerbations and hospitalization, as well as improvements in QoL and no safety concerns [48]. A recent real-life UK study similarly demonstrates positive clinical improvements with long term omalizumab use [49].

Patients with IgE levels higher or lower than the range of 30–700 UI/ml (dependent on the country) and patients who exceed the weight limits are excluded from the omalizumab treatment. However, evidence of omalizumab efficacy in patients who exceed the standard dose recommendation is now emerging. A recent Australian real-life study reports the effectiveness of omalizumab in 55 severe asthmatics above

Table 1 Omalizumab randomized clinical trials

Author (year) [Ref. no.]	Design	Biologic agent	Comparison	Sample size	Study duration	Setting	Outcome measures
Humbert et al. (2005) [22]	Randomized, placebo-controlled, double-blind study	Omalizumab	Omalizumab vs placebo	419 severe persistent asthma (omalizumab = 209; placebo = 210)	28 weeks	108 centers of 14 countries	Exacerbations, hospitalization, ER visit and unscheduled doctor's visits for exacerbations, diary, PEF and use of rescue medication, AQLQ
Hanania et al. (2011) [23]	Prospective, multicenter, randomized, parallel-group, double-blind, placebo-controlled trial	Omalizumab	Omalizumab vs placebo	850 severe asthma (omalizumab = 427; placebo = 423)	48 weeks	193 investigational sites in the United States and 4 sites in Canada	Exacerbations, TASS, puffs per day of albuterol, AQLQ, FeNO, frequency and severity of treatment-emergent AEs, deaths and clinical laboratory evaluations
Gevaert et al. (2013) [24]	Randomized, double-blind, placebo-controlled study	Omalizumab	Omalizumab vs placebo	24 allergic and non-allergic patients with nasal polyps and comorbid asthma (omalizumab = 16; placebo = 8)	20 weeks	University hospitals of Ghent and Leuven, Belgium	Reduction in total nasal endoscopic polyp scores after 16 weeks, sinus CT, nasal and asthma symptoms, results of validated questionnaires (SF-36, RSOM-31, and AQLQ), and serum/nasal secretion biomarker levels
Garcia et al. (2013) [25]	Randomized, placebo-controlled, phase IIIB, double blind study	Omalizumab	Omalizumab vs placebo	41 uncontrolled severe non-atopic asthma (omalizumab = 20; placebo = 21)	16 weeks	10 French centers	FeRI expression on basophils and pDC2s, lung function, ACQ, GETE, AE rates, and FeNO
Pasha et al. (2014) [26]	Randomized, parallel group, double-blind, and placebo-controlled study	Omalizumab	Omalizumab vs placebo	42 patients with moderate-to-severe asthma (omalizumab = 29; placebo = 13)	16 weeks	2 U.S. centers (Albany Medical College Albany, NY, and Creighton University Omaha, NE)	CalvNO
Li et al. (2016) [27]	Randomized, double-blind, parallel-group, placebo-controlled, phase III study	Omalizumab	Omalizumab vs placebo	616 moderate-to-severe persistent allergic asthma (omalizumab = 308; placebo = 308)	24 weeks	China (multicenter)	Morning PEF, FEV1 % predicted, ACQ, ASS and rescue medication use, AQLQ, GETE, and safety

Table 1 (continued)

Author (year) [Ref. no.]	Design	Biologic agent	Comparison	Sample size	Study duration	Setting	Outcome measures
Ledford et al. (2017) [28]	Randomized, double-blind, placebo-controlled withdrawal study	Omalizumab	Omalizumab vs placebo	176 patients with moderate to severe asthma (continuing or withdrawing from omalizumab after ≥ 5 years)	52 weeks	USA	SAE (systemic corticosteroid treatment; hospitalization or ER), ACT, ACQ, FEV1, FeNO, free and total serum IgE concentrations, basophil Fc ϵ RI, frequency and severity of AEs and SAEs, vital signs, and results of clinical laboratory assessments (hematology, serum chemistry, and urinalysis)
Lai et al. (2015) [29]	Systematic review and metaanalysis	Omalizumab	NA	6 RCTs > 52 weeks	NA	NA	Exacerbations, ICS use, GETE, QOL, asthma symptoms, lung function, rescue medication and AEs
Hanania et al. (2013) [30]	Post-hoc analysis of prospective, multicenter, randomized, parallel-group, double-blind, placebo-controlled study	Omalizumab	Low- vs high-biomarker subgroups (FeNO, peripheral blood eosinophils, and serum periostin)	850 patients (omalizumab = 427; placebo = 423)	48 weeks	197 centers in the US and Canada	FeNO, PBE, serum periostin, exacerbations, AQLQ, FEV1, FeNO, AEs, SAEs

ACQ Asthma Control Questionnaire, *ACT* asthma control test, *AEs* adverse events, *AQLQ* Asthma Quality of Life Questionnaire, *ASS* asthma symptom scores, *CalmNO* alveolar nitric oxide concentration, *CT* computed tomogram, *ER* emergency room, *FeNO* exhaled nitric oxide, *FEV1* forced expiratory volume in the 1st second, *GETE* Global Evaluation of Treatment Effectiveness, *ICS* injective corticosteroids, *NA* not applicable, *PBE* peripheral blood eosinophils, *PEF* peak expiratory flow, *QOL* quality of life, *RSOM-31* 31-item rhinosinusitis outcome measuring, *SAEs* serious adverse events (SAEs), *SF-36* Short-Form Health Questionnaire, *TASS* asthma symptom severity

Table 2 Omalizumab observational studies

Author (year) [Ref. no.]	Design	Biologic agent	Comparison	Sample size	Study duration	Setting	Outcome measures
Odajima et al. (2017) [31]	Single-arm, open-label phase III study	Omalizumab	Baseline vs time points	38 severe asthma children	116.6 weeks (range 46.9–151.1 weeks)	15 centers in Japan	AEs and SAEs, JPAC questionnaire, QOL, use of asthma controller medications, spirometry, the number of hospitalizations and ER visits, serum trough concentrations of omalizumab, free and total IgE
Tajiri et al. (2014) [32]	Prospective, single-arm, observational study	Omalizumab	Baseline vs time points	31 severe refractory asthma	48 weeks	Kyoto University Hospital	AQLQ, ACQ, SGRQ, exacerbations, PEF, FeNO, pulmonary function, methacholine airway responsiveness, induced sputum cell count, and chest CT
Nopp et al. (2010) [33]	Observational study (after omalizumab withdrawal)	Omalizumab	Baseline (omalizumab cessation) vs time point (3 years after withdrawal)	18 severe allergic asthmatics (6 years omalizumab treatment); 15 reference group (controlled, mild asthma or rhinoconjunctivitis)	3 years (follow-up)	Karolinska University Hospital, Stockholm, Sweden	Basophil allergen sensitivity (CD-sens), IgE and IgE-and IgG4 antibodies, FEV1, PEF, and a questionnaire
Zazzali et al. (2015) [34]	Observational, prospective study	Omalizumab	Baseline vs time points	7709 moderate-to-severe persistent allergic asthma (Non-omalizumab Cohort = 2779; Omalizumab Cohort = 4930)	5 years	Multiple types of practice settings in a real world setting	ACT, Work, school, activity impairment,
Nopp et al. (2007) [35]	Observational study (after omalizumab withdrawal)	Omalizumab	Baseline (omalizumab cessation) vs time point (6 years after withdrawal)	18 severe allergic asthmatics (6 years omalizumab treatment); 15 reference group (controlled, mild asthma or rhinoconjunctivitis)	6 years (follow-up)	Karolinska University Hospital, Stockholm, Sweden	Basophil allergen sensitivity (CD-sens), IgE and IgE-and IgG4 antibodies, FEV1, PEF, and a questionnaire

Table 2 (continued)

Author (year) [Ref. no.]	Design	Biologic agent	Comparison	Sample size	Study duration	Setting	Outcome measures
Skiepkio et al. (2014) [36]	Observational study	Omalizumab	High decrease in blood eosinophil count (group 1) vs low decrease in blood eosinophil count (group 2)	13 patients with severe persistent allergic asthma (group 1 = 7; group 2 = 6)	12 months	Medical University of Bialystok, Poland	Asthma exacerbations, PBE
Zietkowski et al. (2011) [37]	Observational study	Omalizumab	Omalizumab-treated patients vs control group (patients with conventional therapy)	19 patients with severe persistent allergic asthma (Omalizumab-treated patients = 9; control group = 10)	16 weeks	Medical University of Bialystok, Poland	RANTES in EBC, FeNO, PBE and serum ECP
Zietkowski et al. (2011) [38]	Observational study	Omalizumab	Omalizumab-treated patients vs control group (patients with conventional therapy)	19 patients with severe persistent allergic asthma (Omalizumab-treated patients = 9; control group = 10)	16 weeks	Medical University of Bialystok, Poland	Eotaxin in EBC, FeNO, serum ECP, and PBE
Nopp et al. (2006) [39]	Observational study	Omalizumab	Cd-sens vs CD-max, SPT-sens, nasal provocation titration test, serum IgE and IgE antibody	27 allergic patients with a clinical history of asthma and/or rhinoconjunctivitis	NA	Karolinska University Hospital, Stockholm, Sweden	Allergen threshold sensitivity (CD-sens), maximal percentage CD63 up-regulation at one allergen dose (CD-max) and SPT end-point allergen titration (SPT-sens), nasal provocation titration test, serum IgE and IgE antibody

ACQ Asthma Control Questionnaire, *ACT* asthma control test, *AEs* adverse events, *AQLQ* Asthma Quality of Life Questionnaire, *CT* computed tomogram, *EBC* exhaled breath condensate, *ECP* eosinophil cationic protein, *ER*: emergency room, *FeNO* exhaled nitric oxide, *FEV1* forced expiratory volume in the 1st second, *JPAC* Japanese pediatric asthma control program, *NA* not applicable, *PBE* peripheral blood eosinophils, *PEF* peak expiratory flow, *QOL* quality of life, *SAEs*: serious adverse events (SAEs), *SGRQ* St. George's Respiratory Questionnaire, *SPT* skin prick test

Table 3 Omalizumab real life studies

Author (year) [Ref. no.]	Design	Biologic agent	Comparison	Sample size	Study duration	Setting	Outcome measures
Gibson et al. (2016) [41]	Real life observational study	Omalizumab	Baseline vs time point (6 months)	192 severe allergic asthma with high prevalence of comorbidities	October 2011–June 2014	Australian Xolair Registry (21 clinics)	ACQ-5, AQLQ, daily OCS use
Molinard et al. (2008) [42]	Real life observational study	Omalizumab	Baseline vs time points (6 months, end of April 2006)	146 of severe persistent uncontrolled allergic asthma and one hymenoptera venom allergy	July 2003–January 2006	France	Treatment interruption, date of last clinical evaluation whilst still under treatment, modification of treatments, the number of asthma-related events since the start of omalizumab treatment and undesirable effects
Cazzola et al. (2010) [43]	Real life observational study	Omalizumab	Baseline vs time points	142 patients with uncontrolled severe persistent allergic asthma	12 months	12 Italian Clinical Centers	Asthma-related treatment, exacerbations, ER visits, hospitalization, AEs, GETE
Niven et al. (2016) [44]	Real life observational study	Omalizumab	Comparison between 12 months pre-omalizumab and post-omalizumab initiation	218 adult severe persistent allergic asthma	20 January 2012–1 February 2015	22 UK National Health Service secondary care centers	Change in daily dose of OCS, response to treatment, changes in OCS dosing, exacerbations, lung function, ACT, AQLQ, EQ-5D and hospital resource utilization
Chen et al. (2016) [45]	Real life, retrospective cohort study	Omalizumab	Baseline vs after omalizumab discontinuation (omalizumab therapy over 4 months)	282 patients with moderate to severe asthma	2007–2011	Taiwan National Health Insurance Research Database (NHIRD)	Changes in asthma medication (ICS, LABA + ICS, OCS, SAMA, LAMA), asthma control, frequency of exacerbations and hospitalization rates
Sposato et al. (2016) [46]	Real life observational study	Omalizumab	Baseline vs 1 year treatment across ages	13 severe asthmatics aged 18–39 years; 61 severe asthmatics aged 40–64 years; 31 severe asthmatics aged > 65 years	November 2014–November 2015	18 Italian secondary care centers	Inhaled corticosteroids dosage, SABA on demand therapy, FEV1, ACT, exacerbations

Table 3 (continued)

Author (year) [Ref. no.]	Design	Biologic agent	Comparison	Sample size	Study duration	Setting	Outcome measures
Abraham et al. (2016) [47]	Systematic review of 'Real-life' effectiveness studies	Omalizumab	NA	24 'real-life' effectiveness studies that included 4117 severe allergic asthma patients	NA	NA	Lung function; asthma control and reducing symptomatology; SAEs and associated work/school days lost; reducing healthcare resource utilizations; reducing or discontinuing other asthma medications; improving QOL
Mansur et al. (2017) [49]	Real life observational study	Omalizumab	Comparison between baseline (the 12 months preceding omalizumab therapy) and on-omalizumab treatment (the most recent "latest" 12 months on treatment)	45 severe allergic asthmatics who were treated with omalizumab for longer than 23 months	12 months	The Birmingham Regional Severe Asthma Centre "BRSAS", UK	Acute asthma related general practitioner (GP) visits, ER visits, hospitalizations, use of OCS, ACQ7, FEV1, FeNO, PBE, and work/school days missed
Hew et al. (2016) [50]	Real life observational study	Omalizumab	Omalizumab above-range vs omalizumab within-range (baseline and after 6 months)	179 severe asthmatics (omalizumab above-range = 55; omalizumab within-range = 124)	October 2011–June 2014	Australian Xolair Registry (21 clinics)	ACQ-5, AQLQ, pre- and post-bronchodilator FEV1 per cent predicted
Kupryś-Lipińska et al. (2014) [96]	Real life observational study	Omalizumab	Baseline (omalizumab cessation) vs time points (during the discontinuation of omalizumab)	11 severe asthmatics	3 years	Norbert Barlicki Memorial University Hospital of Lodz, Poland	ACQ, AQLQ, the demand for anti-asthma agents (daily dose of OCS), the occurrence of SAEs and the need for ER visits and hospitalization
Braunstaal et al. (2013) [97]	Real life, international, single-arm, open-label observational study	Omalizumab	Baseline vs time points	943 patients with uncontrolled persistent allergic asthma	2 years	14 countries in Europe, the Americas and Asia	Exacerbation rate, GETE, ACT, ACQ, AQLQ, FEV1, rescue medication use, OCS use, safety

ACQ Asthma Control Questionnaire, ACQ7 Asthma Control Questionnaire 7 items, ACT asthma control test, AEs adverse events, AQLQ Asthma Quality of Life Questionnaire, EQ-5D Euro-QoL-5D, ER emergency room, FeNO exhaled nitric oxide, FEV1 forced expiratory volume in the 1st second, GETE global evaluation of treatment effectiveness, ICS injective corticosteroids, LABA long-acting b2-agonists, LAMA long-acting muscarinic antagonist, NA not applicable, OCS oral corticosteroids, PBE peripheral blood eosinophils, QOL quality of life, SAEs serious adverse events, SABA short-acting b2-agonists, SAMA short-acting muscarinic antagonist

the recommended dosing range [750 (IQR 650–750) mg, without dose escalation above 750 mg] who had a higher baseline IgE [812 (IQR 632–1747) IU/ml]. They show that patients with above-range IgE levels have significant improvements in lung function parameters, symptom control and QoL from pre-omalizumab treatment, similar to patients who receive doses within range [50].

Other anti-IgE under investigation

Despite the positive evidence for the use of omalizumab in severe allergic asthma, approximately one-third of severe asthmatics, 30–39% do not respond to it [19]. Thus, more potent anti-IgE agents were thought essential and investigated: QGE031 (ligelizumab; Novartis, Switzerland) and MEDI 4212 (MedImmune LLC-Gaithersburg, Maryland, USA). Ligelizumab is a humanized IgG1 monoclonal antibody binding the Ce3 domain of IgE with higher affinity than omalizumab and with more effective suppression of basophils/mast cells activity in atopic subjects and mild allergic asthma [18, 51]. However, due to lack of efficacy in a recent study, its progress has been halted (Eudract no: 2012-002298-69; study name CQGE031B2201). MEDI4212 demonstrated an in vitro affinity to IgE 106-fold superior to omalizumab, inducing a more rapid decline in free serum IgE. Moreover, MEDI4212 is able to block the IgE-induced calcium transduction signaling pathways, inhibits IgE activation through the low affinity IgE receptor CD23 [17] and eliminates IgE expressing B cells before their differentiation into IgE secreting cells [52]. Nonetheless, due to the rapid restoring of basal free IgE levels, frequent dosing of these two drugs would be necessary to maintain IgE suppression [18, 53]. Akin to ligelizumab, MEDI4212 studies were interrupted at phase I due to its limitations.

Anti-IL-5

In a particular phenotype of asthma, the TH2/eosinophilic inflammation is considered a hallmark feature of the disease. IL-5 has been shown to have a pivotal role in eosinophil maturation, activation and survival, and targeting eosinophilic/Th2-mediated inflammation; thus antagonizing IL-5 would make a good therapeutic target [54]. Monoclonal antibody therapies neutralizing IL-5 have been recently approved by the FDA (mepolizumab and reslizumab).

Mepolizumab

Mepolizumab is a humanized monoclonal antibody targeting free IL-5 [55–57] that has approved by FDA in November 2015 for use in severe asthma [58]. Mepolizumab studies are summarized in Table 4. Initial studies showed that anti-IL-5 monoclonal antibody therapy attenuated blood, sputum and

bronchial mucosal eosinophils, without significant clinical benefits [59, 60]. Nevertheless, phase IIa studies in severe asthmatics with evidence of eosinophilic inflammation and frequent exacerbations, demonstrate a reduction in exacerbation frequency accompanied by significant attenuation in eosinophilic inflammation [56, 57, 61]. Besides these observations, asthma-related subjective parameters and OCS sparing have also been noted in Phase IIb and III [62–64]. In a post hoc analysis of two RCTs, severe eosinophilic asthma patients previously treated with omalizumab, Mepolizumab is effective and safe [65]. Presently, the evidence for the long-term efficacy and safety of mepolizumab is shown in the COSMOS study, where enrolled patients who received mepolizumab or placebo in MENSA or SIRUS studies show a favorable safety profile after 52 weeks, with a stable and durable response through to 84 weeks [66]. More recently, a DBPC multi-center phase IIIb study (MUSCA) in > 12 year old eosinophilic asthmatics and history of at least one exacerbation in the previous 12 months despite being on high-dose ICS and other controller medications, has assessed health-related QoL over 24 weeks. Compared to placebo, Mepolizumab is associated with a significant improvement in health-related QoL as measured using the St. George's Respiratory Questionnaire (SGRQ) (primary endpoint) and ACQ-5 with a safety profile akin to placebo over the study period. Additionally, marked improvements in various lung function parameters and exacerbation frequency in the favour of Mepolizumab are reported.

Due to the lack of longer term studies, the impact on the immune system with mepolizumab is unclear. Of note the positive benefits on exacerbations and eosinophilic airway inflammation have shown to be reversed within 6 months of mepolizumab withdrawal [56, 67]. Currently there is a lack of studies on mepolizumab in real-life clinical use due to its only recently receiving FDA approval.

Reslizumab

Reslizumab (CINQAIR®; formerly SCH-55700) is a humanized monoclonal antibody that binds with high affinity to circulating IL-5 inhibiting its bioactivity by blocking the IL-5 binding to the alpha chain of IL-5R complex on the eosinophil surface [68]. It was approved by the FDA in March 2016, and is currently administered by intravenous injection, though investigations for a subcutaneous formulation is ongoing [69]. Reslizumab RCTs are summarized in Table 5. Initially, a phase I trial only demonstrated a reduction in blood eosinophil count with no significant improvements in asthma symptoms and lung function [70]. These discouraging results were due to an inadequate patient enrollment in terms of baseline eosinophilia, leading to a more accurate patient selection in the design of subsequent phase II/III clinical trials. In this randomized, double blind, phase II

Table 4 Mepolizumab studies overview

Author (year) [Ref. no.]	Design	Biologic agent	Comparison	Sample size	Study duration	Setting	Outcome measures
Halдар et al. (2009) [56]	Randomized, double-blind, placebo-controlled, parallel-group study	Mepolizumab	Mepolizumab vs Placebo	61 refractory eosinophilic asthmatics	April 2006–August 2008 (50 weeks of treatment)	UK	Number of SAE, AQLQ, FEV1, airway hyperresponsiveness, PBE and sputum eosinophils
Nair et al. (2009) [57]	Randomized, placebo-controlled, double-blind, parallel-group trial	Mepolizumab	Mepolizumab vs placebo	20 severe asthmatics (mepolizumab = 9; placebo = 11)	January 2005–July 2007 (phase 1 = 4 weeks; phase 2 = 22 weeks; phase 3 = 8 weeks)	Clinics of the Firestone Institute for Respiratory Health, Canada	Exacerbations, JACQ, FEV1, quantitative counts of sputum cells and PBE, blood levels of electrolytes, urea, creatinine, alanine and aspartate aminotransferases
Flood-Page et al. (2007) [59]	Multicenter, randomized, double-blind, placebo-controlled study	Mepolizumab	Mepolizumab vs Placebo	362 severe asthmatics (750 mg = 116; 250 mg = 120; placebo = 126)	4 weeks pre-treatment + 12 weeks of treatment + 8 weeks of follow-up	55 centers in 5 countries worldwide	Morning PEF, FEV1, exacerbations, asthma summary symptom scores, use of rescue medication, AQLQ, PBE and sputum eosinophils, pharmacokinetic
Leckie et al. (2000) [60]	Double-blind randomized placebo-controlled trial	Mepolizumab	Anti-IL5 MAb vs Placebo	24 mild allergic asthmatics (placebo = 8; 2–5 mg/kg = 8; 10 mg/kg = 8)	12 weeks	3 centers in UK and 1 in The Netherlands	Blood eosinophil count, sputum eosinophils, airway hyperresponsiveness to histamine, late asthmatic reaction
Pavord et al. (2012) [61]	Multicentre, double-blind, placebo-controlled trial	Mepolizumab	Mepolizumab vs placebo	621 severe eosinophilic asthmatics (placebo = 159; 75 mg = 154; 250 mg = 152; 750 mg = 156)	9 November 2009–5 December 2011	81 centers in 13 countries worldwide	Annual rate of clinically significant exacerbations, ACQ, AQLQ, FEV1, PBE and sputum eosinophils
Bel et al. (2014) [62]	Multicenter, randomized, placebo-controlled, double-blind, parallel-group study	Mepolizumab	Mepolizumab vs placebo	135 severe eosinophilic asthmatics (mepolizumab = 69; placebo = 66)	20 weeks of treatment + 12 weeks of follow-up	38 centers in 10 countries worldwide	Degree of reduction in the glucocorticoid dose, rate of asthma exacerbations, asthma control, and safety
Ortega et al. (2014) [63]	Multicenter, randomized, double-blind, double-dummy, phase III, placebo controlled trial	Mepolizumab	Mepolizumab vs placebo	576 severe eosinophilic asthmatics (75 mg = 191; 100 mg = 194; placebo = 191)	October 2012–January 2014 (run-in period of 1–6; 32-weeks treatment phase; 8-week of follow-up)	119 centers in 16 countries worldwide	Annualized frequency of clinically significant exacerbations, spirometry, hematologic tests, ACQ-5, SGRQ, safety

Table 4 (continued)

Author (year) [Ref. no.]	Design	Biologic agent	Comparison	Sample size	Study duration	Setting	Outcome measures
Ortega et al. (2016) [64]	Post-hoc analysis of data from two randomized, double-blind, placebo-controlled studies	Mepolizumab	Mepolizumab vs placebo	1 192 severe eosinophilic asthmatics (mepolizumab = 846; placebo = 346)	NA	NA	Annual rate of clinically exacerbations, FEV1, hematologic tests, ACQ-5, ACQ-6, SGRQ
Magnan et al. (2016) [65]	Post-hoc analysis of data from two randomized, double-blind, placebo-controlled studies	Mepolizumab	prior omalizumab use vs no-prior omalizumab use	711 severe eosinophilic asthmatics (prior omalizumab use = 120; no-prior omalizumab use = 591)	NA	NA	Annual rate of exacerbations, percentage reduction in OCS dose, FEV1, morning PEF, ACQ-5 and SGRQ scores, PBE, total IgE, and safety
Lugogo et al. (2016) [66]	52-week, open-label extension study of 2 previous double-blind studies	Mepolizumab	Baseline vs time points	651 severe eosinophilic asthmatics	60 weeks	NA	Long-term safety profile, annualized rate of exacerbations, ACQ-5 score, FEV1, OCS dose
Haldar et al. (2014) [67]	Unblinded, prospective, observational study	Mepolizumab	Baseline visit for follow-up vs time points	56 severe eosinophilic asthmatics	12 months	National Institute for Health Research (NIHR) Leicester, UK	Exacerbations, JACO, FEV1, FeNO, sputum and PBE, CT scan

ACQ Asthma Control Questionnaire, ACQ-5 Asthma Control Questionnaire 5 items, ACQ-6 Asthma Control Questionnaire 6 items, AEs adverse events, AQLQ Asthma Quality of Life Questionnaire, FEV1 forced expiratory volume in the 1st second, JACO Juniper Asthma Control Questionnaire, JPAC Japanese pediatric asthma control program, NA not applicable, PBE peripheral blood eosinophils, SAEs serious adverse events, SGRQ St. George's Respiratory Questionnaire

Table 5 Overview of reslizumab randomized control trials

Author (year) [Ref. no.]	Design	Biologic agent	Comparison	Sample size	Study duration	Setting	Outcome measures
Kips et al. (2003) [70]	Randomized, placebo-controlled, phase I pilot study	Reslizumab	Reslizumab vs placebo	32 severe asthmatics (0.03 mg/kg = 2 or placebo = 1; 0.1 mg/kg = 4 or placebo = 1; 0.3 mg/kg = 6 or placebo = 2; 1.0 mg/kg = 12 or placebo = 4)	90 day; 180 days for the 0.3 and 1.0 mg/kg groups	4 centers in Belgium, UK, and the Netherlands	Sputum and blood eosinophil counts, symptom severity, lung function parameters, and physician-evaluated
Castro et al. (2011) [71]	Randomized, double-blind, placebo-controlled, phase II study	Reslizumab	Reslizumab vs placebo	106 severe eosinophilic asthmatics (reslizumab = 53; placebo = 53)	February 2008–January 2010 (15 weeks of treatment)	25 sites in the USA and Canada	ACQ, FEV1, FVC, sputum and PBE, adverse events
Castro et al. (2015) [72]	Randomized, double-blind, parallel-group, placebo-controlled, phase III trial (two duplicate study)	Reslizumab	Reslizumab vs placebo	Study 1 = 489; study 2 = 464	2–4 weeks screening period + 52 weeks treatment period + follow-up visit at 90 days	128 clinical research centers in study 1 and 104 centers in study 2, worldwide	Exacerbation frequency, FEV1, ACQ-7, ASUI, rescue use of SABA, and PBE
Corren et al. (2016) [73]	Randomized, double-blind, placebo-controlled, phase III trial	Reslizumab	Reslizumab vs placebo (sub-analysis between patients with blood eosinophils $\geq 400/\mu\text{L}$ and $< 400/\mu\text{L}$)	496 uncontrolled asthmatics (Reslizumab 3.0 mg/kg = 398; placebo = 98)	16-week double-blind treatment period + 12-week follow-up period	66 study locations across the United States	FEV1, ACQ-7, rescue (SABA) use within the previous 3 days, FVC, blood eosinophils, ACQ-6, AEs
Bjerner et al. (2016) [74]	Randomized, double-blind, placebo-controlled, parallel-group, fixed-dosage, phase III trial	Reslizumab	Reslizumab vs placebo	315 uncontrolled asthmatics with blood eosinophil counts $\geq 400/\mu\text{L}$	16-week double-blind treatment period + 4 weeks after the last infusion	68 sites worldwide	FEV1, FVC, FEF25%-75%, ACQ, ACQ-6, ACQ-5, ASUI, AQLQ, rescue inhaler use, and blood eosinophil count
Brusselle et al. (2017) [75]	Secondary analysis of randomized, double-blind, parallel-group, placebo-controlled, phase III trials [70]	Reslizumab	Reslizumab vs placebo	763 uncontrolled asthmatics (GINA step 4 = 657; GINA step 5 = 106)	2–4 weeks screening period + 52 weeks treatment period + follow-up visit at 90 days	128 clinical research centers in study 1 and 104 centers in study 2, worldwide	FEV1, ACQ-7 score and AQLQ score

ACQ Asthma Control Questionnaire, ACQ-5 Asthma Control Questionnaire 5 items, ACQ-6 Asthma Control Questionnaire 6 items, AEs adverse events, AQLQ Asthma Quality of Life Questionnaire, FEV1 forced expiratory volume in the 1st second, JACQ Juniper Asthma Control Questionnaire, JPAC Japanese pediatric asthma control program, PBE peripheral blood eosinophils, SAEs serious adverse events, SGRQ St. George's Respiratory Questionnaire

trial, severe asthma patients with induced sputum eosinophil $\geq 3\%$ were enrolled. Reslizumab (3 mg/kg) and placebo were injected once every 4 weeks for 15 weeks. A significant improvement in FEV₁ and a reduction in both sputum and blood eosinophil count are reported in the patients treated with reslizumab compared to placebo [71]. Two duplicate phase III trials with reslizumab confirm reduction in asthma exacerbations, improvements in health status and asthma control [72]. Improvements in asthma control are associated with higher baseline blood eosinophil counts (≥ 400 cells/ μ l). In asthmatic patients with blood eosinophil count ≥ 400 cells/ μ l and uncontrolled on ICS-based regimen, treatment with reslizumab 3.0 mg/kg improves lung function, asthma symptoms, and QoL [73, 74]. Of note, reslizumab treatment in asthmatics with a blood eosinophil count < 400 cells/ μ l does not seem to improve asthma outcomes [73]. A recent secondary analysis of pooled data from the two duplicate phase III data [72] was performed to assess the efficacy of reslizumab in patients receiving asthma treatment on Step 4 and Step 5 of the GINA guidelines at baseline. Reduction in exacerbation rates, and improvements in lung function and patient-reported outcomes (ACQ-7; AQLQ) are shown in patients treated with reslizumab [75]. The safety of reslizumab has also been demonstrated in several RCTs [70–72, 74, 75]. Furthermore, reslizumab has been shown to be effective in specific subgroups of patients with eosinophilic asthma; particularly in patients with nasal polyposis [71, 76], and increased severity [77, 78]. This may aid clinicians to focus on asthma patients who might be responsive to reslizumab.

Other biologic drugs in phase III evaluation

Currently, there are only two biological agents under phase III evaluation studies, promising for the treatment of moderate-to-severe asthma: Benralizumab (MEDI-563; AstraZeneca, UK) and Dupilumab (REGN668/SAR231893; Sanofi and Regeneron cooperation). The studies on these molecules are summarized in Table 6.

Benralizumab

Benralizumab is a human afucosylated monoclonal antibody that targets the IL-5 receptor α (IL-5R α) expressed on eosinophils and basophils, inducing direct, rapid and nearly complete depletion of eosinophils via ADCC [79]. A small phase I DBPC trial performed in severe eosinophilic asthmatics (sputum eosinophils $\geq 2.5\%$), shows that benralizumab decreases airway mucosal and sputum eosinophils in addition to a completely suppressing blood and bone marrow eosinophils, and their precursors when compared with placebo [80]. In a Phase IIa study, benralizumab shows a

significant reduction in exacerbation rates, improvements in lung function and asthma control in severe asthmatics with a high baseline blood eosinophil count [81]. Two multicenter RCTs phase III studies (SIROCCO and CALIMA) have been performed to assess the efficacy and safety of benralizumab, as add-on therapy, and define the patient population with greatest benefit from the treatment [82, 83]. In both studies severe uncontrolled asthma patients were treated with benralizumab 30 mg either every 4 weeks (Q4W) or every 8 weeks (Q8W) for 48 weeks (SIROCCO) and 56 weeks (CALIMA); patients were also stratified in two subgroups by baseline blood eosinophil count ≥ 300 cells/ μ l and < 300 cells/ μ l. The results from the SIROCCO and CALIMA studies show that benralizumab treatment (Q4W and Q8W) attenuates annual exacerbation rates, blood eosinophil counts and improves lung function in severe uncontrolled asthma patients with elevated blood eosinophils. Only the Q8W regimen significantly improves asthma symptoms compared to placebo. Reduced annual exacerbation rates and blood eosinophils are also observed in patients receiving high doses of ICS plus LABA with baseline blood eosinophil counts < 300 cells/ μ l. An analysis of the SIROCCO and CALIMA studies was performed to characterize the patient population most likely to benefit from benralizumab treatment [84, 85]; an initial analysis confirms the efficacy and safety of benralizumab in severe asthmatics with blood eosinophil counts ≥ 150 cells/ μ l [84]. A subsequent pooled analysis of these studies expanded the potential patient population who might be responsive to benralizumab. Indeed, patient stratification was performed by baseline blood eosinophil counts stratification (≥ 0 , ≥ 150 , ≥ 300 , or ≥ 450 cells/ μ l) and history of exacerbation. Patients with blood eosinophil counts ≥ 0 cells/ μ l who were treated with benralizumab every 4 or 8 weeks show reduced annual exacerbation rate, increased FEV₁, and improved asthma symptoms compared with placebo. Furthermore, patients with a history of frequent exacerbations (≥ 3 in the previous 12 months) have greater efficacy with benralizumab treatment than do patients with fewer exacerbations (< 3 in the previous 12 months) [85]. Moreover, Nair and colleagues (ZONDA study) recently report that add-on benralizumab therapy significantly reduces the OCS dosage in severe asthma patients [86]. Further, evaluations and confirmation of benralizumab efficacy and safety in eosinophilic severe asthma are underway in other ongoing phase III studies (NCT02869438 [87]; NCT03186209 [88]; NCT03170271 [89]).

Dupilumab

Dupilumab is a human monoclonal antibody currently in phase III investigation for moderate-to-severe asthma. This biologic agent is directed against the alpha subunit of the IL-4 receptor (IL-4R α) and inhibits the IL-4 and IL-13

Table 6 Other biologic drugs: randomized controlled trials overview

Author (year) [Ref. no.]	Design	Biologic agent	Comparison	Sample size	Study duration	Setting	Outcome measures
Laviolette et al. (2013) [80]	Multicenter, double-blind, placebo-controlled phase I study	Benralizumab	Benralizumab vs placebo	Cohort 1 (asthmatics who received single iv dose: placebo or benralizumab) = 13; cohort 2 (asthmatics who received multiple dose: placebo or benralizumab) = 14	Cohort 1 = follow-up 28 and 84 days; cohort 2 = 56 days of treatment + 28 days of follow-up	3 United States and 4 Canadian medical centers	Airway mucosal/submucosal eosinophils, sputum eosinophils, bone marrow eosinophils and neutrophils, PBE and basophils, AEs, SAEs
Castro et al. (2014) [81]	Randomised, controlled, dose-ranging phase IIb study	Benralizumab	Benralizumab vs placebo	324 eosinophilic asthmatics (placebo = 80; 2 mg benralizumab = 81; 20 mg dose = 81; 100 mg dose = 82) and 285 non-eosinophilic asthmatics (100 mg benralizumab = 142, 140 included in analysis; placebo = 143, 142 included in analysis)	3 January 2011–6 March 2012 (52 weeks)	33 sites worldwide	Annual exacerbation rate in eosinophilic individuals after 1 year of follow-up, FEV1, mean ACQ-6 score, overall symptom score, mean AQLQ, FeNO, PBE
FitzGerald et al. (2016) [82]	Randomised, double-blind, parallel-group, placebo-controlled, phase III study (CALIMA)	Benralizumab	Benralizumab vs placebo	1306 severe uncontrolled asthmatics (30 mg Q4W = 425; 30 mg Q8W = 441; placebo = 440)	56 weeks	303 sites in 11 countries	Annual exacerbation rate, pre-bronchodilator FEV1, post-bronchodilator FEV1; ACQ-6 score; and AQLQ(S) + 12 score, AEs
Bleecker et al. (2016) [83]	Randomised, double-blind, parallel-group, placebo-controlled, phase III study (SIROCCO)	Benralizumab	Benralizumab vs placebo	1205 severe uncontrolled asthmatics (placebo = 407; 30 mg Q4W = 400; 30 mg Q8W = 398)	48 weeks	374 clinical research centers worldwide	Annual exacerbation rate, pre-bronchodilator FEV1, post-bronchodilator FEV1; ACQ-6 score; and AQLQ(S) + 12 score, AEs, and SAEs

Table 6 (continued)

Author (year) [Ref. no.]	Design	Biologic agent	Comparison	Sample size	Study duration	Setting	Outcome measures
Goldman et al. (2017) [84]	Pooled analysis of two randomised, double-blind, parallel-group, placebo-controlled, phase III study	Benralizumab	Benralizumab (Q8W regimen) vs placebo	1456 severe uncontrolled asthmatics (SIROCCO study: ≥ 150 cells/ μ L $n = 631$; < 150 cells/ μ L $n = 122$) (CALIMA study: ≥ 150 cells/ μ L $n = 615$; < 150 cells/ μ L $n = 88$)	NA	NA	Annual exacerbation rate, pre-bronchodilator FEV ₁ , post-bronchodilator FEV ₁ ; ACQ-6 score; and AQLQ(S) + 12 score, AEs, and SAEs
FitzGerald et al. (2017) [85]	Pooled analysis of two randomised, double-blind, parallel-group, placebo-controlled, phase III study	Benralizumab	Benralizumab vs placebo (analyzed by baseline eosinophil counts ≥ 0 , ≥ 150 , ≥ 300 , or ≥ 450 cells/ μ L, and by number of exacerbations)	2295 severe uncontrolled asthmatics	NA	NA	Annual exacerbation rate, pre-bronchodilator FEV ₁ , post-bronchodilator FEV ₁ ; ACQ-6 score, AQLQ(S) + 12 score
Nair et al. (2017) [86]	Randomized, double-blind, parallel-group, placebo-controlled, phase III trial	Benralizumab	Benralizumab vs Placebo	220 severe uncontrolled asthmatics (placebo = 75; Q4W = 72; Q8W = 73)	28 weeks	91 sites worldwide	Percentage change in the OCS dose, annual asthma exacerbation rate, the time to the first asthma exacerbation, the percentage of patients with at least one asthma exacerbation, FEV ₁ , ACQ-6 score, AQLQ(S) + 12 score, AEs
Wenzel et al. (2016) [91]	Randomized, double-blind, placebo-controlled, parallel-group, pivotal phase IIb clinical trial	Dupilumab	Dupilumab vs placebo	769 patients (placebo = 158; dupilumab groups = 611)	24 weeks of treatment + 16 weeks post-treatment	174 sites worldwide	FEV ₁ , ACQ-5, AQLQ, FeNO, blood eosinophil count, AEs, SAEs

ACQ Asthma Control Questionnaire, ACQ-5 Asthma Control Questionnaire 5 items, ACQ-6 Asthma Control Questionnaire 6 items, AEs adverse events, AQLQ Asthma Quality of Life Questionnaire, FeNO exhaled nitric oxide, FEV₁ forced expiratory volume in the 1st second, JACQ Juniper Asthma Control Questionnaire, JPAC Japanese paediatric asthma control program, NA not applicable, OCS oral corticosteroids, PBE peripheral blood eosinophils, Q4W 30 mg every 4 weeks, Q8W 30 mg every 8 weeks, SAEs serious adverse events, SGRQ St. George's Respiratory Questionnaire

signal transduction [90]. During phase IIb trial, dupilumab shows significant efficacy and a favorable safety profile in a wide range of patients with uncontrolled persistent asthma regardless of baseline blood eosinophil count [91]. Currently, three phase III trials are ongoing to evaluate dupilumab efficacy and safety in adult and adolescent with persistent asthma on medium to high dose of ICS plus a second controller (NCT02414854) [92], severe steroid-dependent asthma (NCT02528214) [93], also in the long-term (NCT02134028) [94].

Discussion

Most of the discussion section is based on omalizumab with its extensive use in routine clinical practice. More experience with anti-IL-5 agents is necessary and awaited. Importantly, the challenges of omalizumab use are a useful guide for these new biological agents; their use needs to be with caution, especially with regards to the costs and also any potential safety issues.

Omalizumab, in the recent years has presented both as a game-changer molecule and as an option in the therapeutic arsenal in the field of asthma or allergic diseases. Although it is indicated in treating severe asthmatics allergic to perennial allergens, Domingo et al. show a significant decrease of annual exacerbation rate and methyl-prednisolone use, both in severe asthma caused by seasonal and perennial allergens [95]. Furthermore, there is evidence in the literature of the efficacy of anti-IgE agents in non-allergic asthma; the underlying mechanisms of benefit remain unclear though hypotheses have been generated [24, 25]. Positivity to an unidentified antigen, such as *Staphylococcus Aureus* (*S. Aureus*) superantigen, may be responsible for the local polyclonal IgE production. Furthermore, the finding in bronchial biopsies from non-atopic asthmatic patients of enhanced expression of Th2-type cytokines (IL-4, -5, and -13) and FcεRI compared with control subjects, support the hypothesis of a local bronchial, mucosal, IgE-class-mediated inflammation, and omalizumab response, notwithstanding negative RAST and skin prick-test to common aeroallergens [25]. Findings of efficacy in non-atopic and also in seasonal allergen asthmatics puts omalizumab mechanism of action into question. Does omalizumab only work by attenuating the IgE levels or are there alternative mechanisms involved? Identifying these would be pivotal to not only treating patients with non-atopic conditions, including asthma.

Additionally, there is ongoing debate, on omalizumab therapeutic role for prolonged periods. Despite its efficacy [17–22, 27, 29, 31, 42, 43, 47], good safety profile [27, 29, 31, 49] and cost effectiveness as add-on therapy in patients with severe atopic asthma [28, 33, 96, 97], questions about its management in the clinical setting still remain

unanswered. Many patients start omalizumab treatment with good results in terms of asthma control and exacerbation rate, though during the course of therapy maintaining a high compliance rate may be challenging, as patients need to attend hospital every 2-to-4 weeks for their injections, with an augmented rate of skipped administration. The other controversial point is its dosage and duration of therapy, indeed it is unclear if it is appropriate to continue long term with omalizumab treatment based on baseline serum IgE levels, and whether it may be used as attack therapy or not. Evidence shows that over time the suppression of IgE binding to their receptors (FcεRI and FcεRII) decreases the reactivity of basophils and mast cells, and also the production and secretion of IgE by plasma cells [21]. With these challenges and increasing clinical use of omalizumab there is an increasing need for functional, cellular or biochemical markers (or a set of markers) to fine tune the doses of drug needed for individual patients over time and for how long, if not long term. Additionally, it may be useful to define a molecular/functional algorithm that aids the specialist to decide the optimal biologic therapeutic approach for a specific patient.

Prior to long term omalizumab treatment, patients should be monitored for treatment response at 16 weeks of treatment [47, 98], after which responders have been suggested to continue treatment for 2–4 years [47]. The method used to define whether a patient is a responder or a low/non-responder [48] may be another critical point that would be better handled with the use of predictive biomarkers. The low/non-responders asthmatics to omalizumab prevalence is considered to be up to one-third of patients [20], which is a substantial number of patients undergoing 16 weeks of therapy resulting in a significant amount of economic resources that might potentially be saved by use of predictive biomarkers.

Importantly, there is no appropriate time to discontinue omalizumab treatment in responsive patients. Following withdrawal of omalizumab after 4–6 years of treatment its beneficial effects seems to persist in a number of patients [28, 33, 35]. Nevertheless, some reports suggest that the withdrawal of omalizumab therapy after a successful long-term therapy in patients with a long history of severe atopic asthma associated with high doses of systemic corticosteroids may result in severe asthma exacerbations [17, 96]. In such situations, a clinical or biological marker may be vital in identifying the immunological changes in patients during omalizumab treatment that could help to better define the appropriate time to interrupt or reduce treatment for individual patients, hence reducing the risks for a relapse.

Clinical and functional parameters have been shown to be improved with omalizumab treatment. Spirometric parameters may improve after a few months of therapy [97], and also inflammatory markers may ameliorate, including

eosinophil counts both in peripheral blood and induced sputum [36, 99]. However, there is a lack of consistency in the relationship between the patient's condition, inflammatory status of the lungs and the reactivity of the immune system, hence making it a challenge to use them as objective parameters to assess the stability of the efficacy of therapy [36]. Likewise, the surrogate marker of airway inflammatory status, FeNO, does not always correlate with omalizumab therapy efficacy [100]. Other surrogate markers in exhaled breath condensate (EBC) have been investigated [37, 38], though they still require confirmation and comprehension in their interpretation as assessment or management tools for patients on omalizumab therapy. Work by Nopp and colleagues observes that after a 6 year period of omalizumab treatment followed by 1 and 3 years of its withdrawal, clinical and functional patient parameters of patients remain comparable to those seen prior to therapy with omalizumab [33, 35]. They also demonstrate that the basophil allergen threshold sensitivity or CD-sensitivity (CD-sens) may be a useful approach to anti-IgE treatment efficacy evaluation [39] and in general to an anti-allergic treatment. It seems to be a reliable biomarker that may be helpful in the evaluation of the severity of allergic reactions, and thus of inflammation induced by the allergic reactions, though larger studies are needed to understand its use in the clinical management of anti-allergic therapies.

Despite the positive subjective, objective and exacerbation data in severe eosinophilic asthmatics, the experience with mepolizumab is limited. Real-life studies able to identify novel predictive biomarkers of response to treatment that will help us to select accurately patients who may benefit from this therapy, and to monitor the progress in controlling the disease and exacerbation still remain to be identified. Additionally these biomarkers may aid in defining the timing of the treatment, since persistent inhibition of IL-5 function and eosinophils in the long term, may expose patients to other risks, such as parasite infections or immune response deregulation.

Indeed, there are severe asthma patients who are eligible for both mepolizumab and omalizumab therapy [58]. Cockle and colleagues performed a systematic review with an indirect treatment comparison between mepolizumab and omalizumab effectiveness in severe asthma. Despite several limitations owing to a limited number of studies and residual heterogeneity, the analysis provides evidence that mepolizumab seems to be at least effective and tolerated as well as omalizumab [59].

At present, despite extensive data on efficacy and safety on omalizumab, there remain a number of unanswered questions. Importantly, the certainty of new more potent anti-IgE therapies to overcome omalizumab shortfalls are in question, and other new anti-inflammatory biological strategies under evaluation have shown good efficacy and initial safety

outcomes (besides the newly licensed mepolizumab and reslizumab).

Conclusions

Summarizing the overall results discussed above, to-date we have two possible biological options to treat inhaled therapy-resistant asthma, which works on two different pathways, IgE- and eosinophils/IL-5-mediated pathways. The reports with anti-IgE and anti-IL-5 both describe successful outcomes in clinical and biological parameters of asthmatic patients. The most extensive experience in the clinical setting is with the use of omalizumab, as it was the only biologic approved globally for use in patients with severe atopic asthma for over a decade. However, there remain some limitations in its use. Importantly, both these drug classes have an excellent safety profile, with the adverse effects, if present, mild and self-limiting, and if more severe resolved by drug withdrawal. It is pivotal to select the appropriate drug for each individual patient phenotype, as it has an impact not only on the management of their clinical condition but also the individual's biological profile. Attention needs to be devoted to novel emerging approaches to severe asthma treatment. The introduction of these 'biological weapons' in the arsenal at our disposal to target specific inflammatory pathways in various chronic diseases, including that in severe asthma, is a revolution in the management of these conditions.

Compliance with ethical standards

Conflict of interest None.

Statement of human and animal rights This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent None.

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