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Review

Prediction of response to biological treatment with monoclonal antibodies in severe asthma

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ABSTRACT

In recent years, major developments have occurred in severe asthma management. Different asthma phenotypes and subgroups have been identified and new treatment options have become available. A total of five monoclonal antibodies are currently approved in severe asthma treatment: omalizumab, mepolizumab, reslizumab, benralizumab and dupilumab. These drugs have been shown to reduce exacerbations and to have an oral corticosteroid-sparing effect in many severe asthma patients. However, biological treatment is not successful in all patients and should be discontinued in non-responsive patients. Treating the right patient with the right biologic, and therefore biologic response prediction, has become a major point of interest in severe asthma management. A variety of response outcomes is utilized in the different clinical trials, as well as a huge range of potential predicting factors. Also, regarding the timing of the response evaluation, there are considerable differences between studies. This review summarizes the results from studies on predicting responses and responders to biological treatment in severe asthma, taking into account clinical, functional and inflammatory parameters assessed prior to the start of treatment as well as following a few months of therapy. In addition, future perspectives are discussed, highlighting the need for more research to improve patient identification and treatment responses in the field of biological treatment in severe asthma.

1. Introduction

Patients with severe asthma require high-dose inhalation therapy to control their disease. These patients experience frequent exacerbations, and they often depend on the chronic use of oral corticosteroids (OCS) with associated serious adverse effects.[1] In recent years, major developments occurred in severe asthma management. Different asthma phenotypes and subgroups were identified [2] and new treatment options have become available in the form of monoclonal antibodies (MABs).[3] Although these novel biological agents have shown promising results in many patients with asthma, it is evident that not all patients respond equally well. This difference in treatment response may be multifactorial and related to the heterogeneity of the severe asthma population or the different underlying molecular pathways, but also drug and treatment strategy related factors may play a role. Optimal use of biologics, both in terms of costs and prevention of unnecessary patient exposure, is of the utmost importance. A Dutch cost estimation indicates the drug costs per patient per year in the Netherlands at €15.000,-.[4] Unfortunately, it is not yet clear which patients will respond to which biologic. Therefore, biologic response prediction has become a major point of interest in severe asthma management.

The present article shortly describes asthma phenotypes, and inflammatory mechanisms and pathobiologic features leading to severe asthma. Furthermore, the pharmacological mechanism of action and clinical outcomes of the currently available biologics for severe asthma are summarized. Then, we thoroughly review predictors of response to the currently registered biologics and, finally, discuss recent developments and future perspectives in response prediction.

2. Asthma subtypes and pathobiology

Asthma is a heterogeneous, inflammatory airway disease in which different phenotypes have been identified based on clinical, functional or inflammatory parameters.[2] Late-onset eosinophilic asthma is currently one of the most well-defined asthma phenotypes with a clearly

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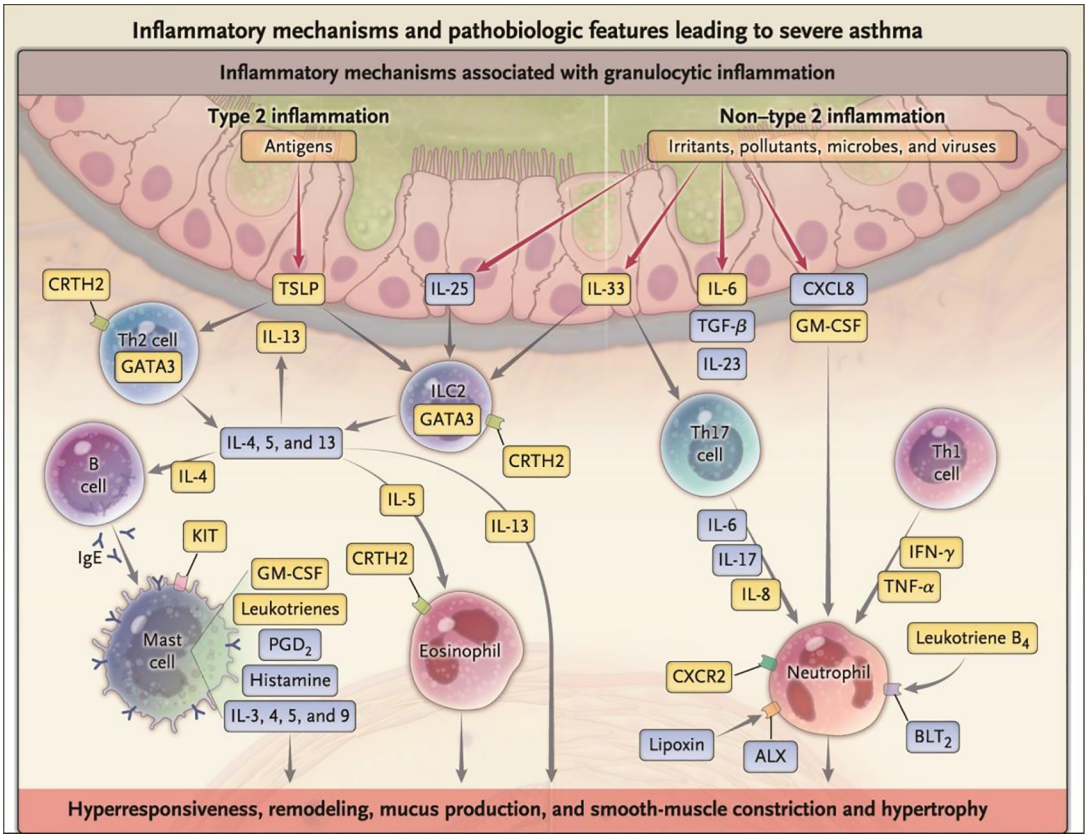

Fig. 1. Inflammatory mechanisms leading to severe asthma. Abbreviations: TSLP = thymic stromal lymphopoietin, IL = interleukin, Th2 = T-helper 2, ILC2 = innate lymphoid cell 2, IgE = immunoglobulin E. Triggering factors (antigens, pollutants) activate the airway inflammation cascade via epithelial-produced factors (TSLP, IL-25 and IL-33). Th2 and ILC2 activation leads to IL-4, IL-5 and IL-13 production. B-cell activation by IL-4 leads to IgE release in allergic asthma, while IL-5 leads to eosinophil recruitment, migration and activation. In collaboration with these factors, IL-13 leads to airway hyperresponsiveness, remodeling, mucus production and smooth-muscle contraction and hypertrophy. Adapted from The New England Journal of Medicine, Elliot Israel, Helen K. Reddel, Severe and Difficult-to-Treat Asthma in Adults, 377, 965 Copyright © (2017) Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

different clinical profile from that seen in classic childhood-onset allergic asthma.[5] Patients with late-onset eosinophilic asthma show eosinophilic inflammation in blood as well as sputum and frequently report absence of atopy, chronic rhinosinusitis with nasal polyposis as comorbidity and a good response to systemic corticosteroids.[6] Both phenotypes are associated with so-called type 2 inflammation.[7–9] In addition to these two type 2 phenotypes, there is a heterogeneous group of patients without evidence of type 2 inflammation.

Type 2 inflammation (Fig. 1[7]) is mainly characterized by the presence of type 2 cytokines (Interleukin (IL)-4, IL-5 and IL-13) and eosinophilia.[7,9,10] In allergic asthma, antigens are presented to naïve T-cells by dendritic cells, converting them to T-helper (Th)2-cells.[11,12] In addition, epithelial cells produce thymic stromal lymphopoietin (TSLP) when triggered by antigens, promoting the Th2-cell conversion and innate lymphoid cells-2 (ILC2s) activation.[13,14] The cytokine production by Th2-cells (IL-4, IL-5 and IL-13[9,10]) and ILC2 cells (IL-5 and IL-13[15]) is regulated by transcription factor GATA-3.[16–18]

IL-4 and IL-13 were amongst the first cytokines that were identified as important drivers of type 2 inflammation. IL-4 stimulates B-cell isotope switching, leading to immunoglobulin E (IgE) production.[19,20] Binding of IgE on the high-affinity IgE receptor (FcεRI) on mast cells and basophils leads to the production of multiple mediators and cytokines that cause airway smooth muscle contraction, remodeling, eosinophilic infiltration and amplification of the inflammatory cascade.[7,21–23] IL-13 stimulates airway epithelium to promote enhanced mucus production and goblet cell hyperplasia and also acts on smooth muscle cells inducing hyperresponsiveness and remodeling.[24,25] There is a close link between IL-4 and IL-13 activity because both activate the alpha subunit of the IL-4 receptor (IL-4Rα).[26,27]

IL-5 is an essential cytokine in promotion, migration, maturation and survival of eosinophils.[23,28] Eosinophils are able to degranulate, releasing cytotoxins with antimicrobial effects as well as potency to damage host tissue. But especially their immune-modulatory capacity, involving the innate as well as the adaptive immune system, seems to play an important role, promoting a type 2 inflammatory environment in the lungs.[24]

In non-allergic asthma ILCs play a major role. Non-allergic triggers, such as pollutants, irritants or microbes, stimulate the airway epithelial cells to produce TSLP, IL-33 and IL-25. ILCs are activated by these cytokines to ILC2s which produce IL-5 and IL-13, leading to the before mentioned effects on the airways.[9]

2.1. Biologics: mechanism of action

Five biologics are currently registered in the EU for the treatment of severe asthma, all targeting type 2 inflammation. There are currently no effective and safe biologics available for non-type 2 asthma. Structural information and fasta-sequences are displayed in Table 1. Unfortunately, no crystallographic information is available in the public domain. In 2003 omalizumab was registered for the treatment of moderate-to-severe allergic asthma. Omalizumab binds IgE, preventing its function in binding and activating the FcεRI.[34] In 2014 mepolizumab was registered for the treatment of severe eosinophilic asthma. Mepolizumab binds free serum IL-5, preventing it from binding and

Table 1
Overview of biologic structural information.

Biologic	Type	Fasta-sequence
Omalizumab[29]	Humanized immunoglobulin-G1κ	**Heavy chain** EVQLVESGGGLVQPGGSLRLSCAVSGYSITSGYSWNWIRQAPGKGLEWVASITYDGSTNYADSVKGRFTISRDDSKNTFYLQMNSLRAEDTAVYYCA- RGSHYFGHWHFAVWGQGTLVTVSSGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLG- TQTYICNVNHKPSNTKVDKKAEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKP- REEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPE- NNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK **Light chain** DIQLTQSPSSLSASVGDRVTITCRASQSVDYDGDSYMNWYQQKPGKAPKLLIYAASYLESGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSHE- DPYTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNR
Mepolizumab[30]	Humanized immunoglobulin-G1κ	N/A
Reslizumab[31]	Humanized immunoglobulin-G4κ	N/A
Benralizumab[32]	Humanized immunoglobulin-G1κ	**Heavy chain** EVQLVQSGAEVKKPGASVKVSCKASGYTFTSYVIHWVRQRPGQGLAWMGYINPYNDGTKYNERFKGKVTITSDRSTSTVYMELSSLRSEDTAVYLCG- REGIRYYGLLGDYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPS- SSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNA- KTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESN- GQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK **Light chain** DIQMTQSPSSLSASVGDRVTITCGTSEDIINYLNWYQQKPGKAPKLLIYHTSRLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQGYTLPYT- FGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
Dupilumab[33]	Humane immunoglobulin-G4	**Heavy Chain** EVQLVESGGGLEQPGGSLRLSCAGSGFTFRDYAMTWVRQAPGKGLEWVSSISGSGGNTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCA- KDRLSITIRPRYYGLDVWGQGTTVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVV- TVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHN- AKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWES- NGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLG **Light Chain** DIVMTQSPLSLPVTPGEPASISCRSSQSLLYSIGYNYLDWYLQKSGQSPQLLIYLGSNRASGVPDRFSGSGSGTDFTLKISRVEAEDVGFYYCMQAL- QTPYTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

Listed are the biologics, biologic type and fasta-sequence. Abbreviation: N/A = not available.

activating the alpha chain of the IL-5 receptor complex on eosinophils. [35] Reslizumab was registered in 2017 and has the same mechanism of action as mepolizumab.[36] In 2017, the third IL-5 targeting biologic, benralizumab, was registered, which binds the alpha chain of the IL-5 receptor on eosinophils, preventing IL-5 binding and subsequently eosinophil activation. Furthermore, the constant heavy chain 2 part of the Fc-region of benralizumab lacks fucose sugar residue, greatly enhancing it's affinity to the FcγRIIIa receptors on natural killer (NK)-cells and macrophages, leading to antibody-dependent cell-mediated cytotoxicity, depleting the number of eosinophils.[37,38] Finally, dupilumab is the fifth biologic, registered in 2018 for severe eosinophilic asthma. Dupilumab binds the alpha subunit of the IL-4 receptor, preventing the function of both IL-4 and IL-13.[39]

2.2. Biologics: outcome measures

Different outcome measures are used in the distinct randomized clinical trials (RCTs) and also regarding the timing of the treatment evaluation, there are considerable differences between studies. An overview of outcome measures and treatment effects for the different biologics in severe asthma was constructed, summarizing the results for the primary outcomes of the biologic pre-approval phase III trials (Table 2). Reduction of exacerbation rate (7 RCTs), OCS dose reduction (3 RCTs), and improvement in lung function (2 RCTs) were found as primary outcomes, indicating the different treatment targets in severe asthma. Study duration varied from 16 to 53 weeks, and 3 of these RCTs included an evaluation moment between study start and end.

3. Predictors of response

The main objective of phase I-III clinical trials is the assessment of efficacy and safety. Knowing which patient will respond in real-life is a different objective and usually not established at the moment of market approval of the biologic. Prediction of treatment responses is not easy and has to deal with various problems: e.g. how to define a response or responder, what are clinically relevant outcome measures [51], and what should be the timing of the evaluation of response. Since currently an overview on the topic is lacking, a summary of the results from studies concerning predicting responses and responders to biological treatment in severe asthma is given. References were extracted from the MEDLINE and EMBASE database until 1 December 2019.

Several of these studies have defined responders to therapy, using different responder criteria and different time points of evaluation, mostly addressing positive outcomes in global evaluation of treatment effectiveness (GETE)[52], exacerbation rate, or lung function tests evaluated after 4–12 months of treatment. More often the possibility to predict separate outcomes was investigated using data collected at baseline (before start biologic) or at an early evaluation some months after start of therapy. The different studies will be discussed below. Table 3 gives an overview of the largest studies (≥100 participants) regarding predictors and outcomes, for responders as well as responses to biological treatment.

3.1. Omalizumab

Most experience has been gained with the prediction of response of omalizumab, since it was the first MAB that was introduced and registered for the treatment of asthma (2003). Omalizumab is given in 75–600 mg subcutaneous injections. Advantages of omalizumab are the long experience and expertise that have been gained over the years and the specific applicability for allergic patients. The dosing regime is based on baseline serum IgE-level and bodyweight. In selecting treatment eligible patients, an IgE cut-off value of ≥ 30 IU/mL is utilized. [53]

Omalizumab: baseline characteristics to predict medium and long term response

The PROSPERO trial is the only large, prospective, real-world observational trial in asthma patients receiving biological treatment (omalizumab) which was aimed at prediction of response. Patients were evaluated after 48 weeks of omalizumab treatment and considered omalizumab responders when they achieved an annual exacerbation reduction ≥ 50%, asthma control test (ACT) improvement to ≥ 20 of 3 point improvement or Forced Expiratory Volume in 1 s (FEV1) improvement ≥ 120 mL. 78% of 795 patients met at least one of these criteria and were characterized as responders, the majority of them by an exacerbation reduction of ≥ 50%, whereas 23% were responders in all categories. In the responder analysis, females and patients with a positive allergen-specific IgE test were more likely to be responders (using all 3 criteria). Patients with high eosinophil levels were more likely to be ACT-responders. Lung function responders had poorer asthma control (ACT < 20) at baseline. Aside from female gender, an increased number of exacerbations 12 months before baseline was the only factor associated with being responder by exacerbation definition. [54]

Clinical and functional parameters

Two commonly used validated questionnaires in asthma-care are the Asthma Control Questionnaire (ACQ) and the Asthma-related Quality of Life Questionnaire (AQLQ).[55,56] An Australian registry study in 180 patients studied the omalizumab responder rate, assessed by an improvement of at least 0.5 in ACQ-5 after 6 months of treatment, and they found poor asthma control (baseline ACQ-5 ≥ 2.0) and older age to be predictive.[57] A small (n = 41) Greek single centre study explored clinical and inflammatory characteristics that could predict response to omalizumab and divided patients into early responders (improved within 16 weeks), late responders (improved between 16 and 32 weeks), or non-responders (no improvement at 32 weeks). They used GETE as responder criterion, and found that lower baseline FEV1 and higher IL-13 levels in induced sputum supernatant were predictors of response to omalizumab. Only three patients came out as late-responder, making an analysis into predictors of late responders unfeasible.[58]

Inflammatory parameters

Several inflammatory markers have been supposed to be possibly predictive of omalizumab response. While several of these markers are only used experimentally, some of them are parameters that are used in daily practice, i.e. blood eosinophils, IgE, fraction of exhaled nitric oxide (FeNO), and (in specified centres) periostin. Nitric oxide is produced by endothelial nitric oxide synthases in case of airway-inflammation and FeNO is used as a non-invasive biomarker of type 2 airway inflammation.[59] Periostin is induced by airway epithelial cells and fibroblasts in response to IL-13 and is therefore considered a biomarker for IL-13 driven inflammatory processes.[60]

To determine the importance of pre-treatment blood eosinophil count as a predictive measure for response to omalizumab, the retrospective STELLAIR study included 723 adult patients, and compared omalizumab effectiveness in patients with high (≥ 300 cells/μL) and low (< 300 cells/μL) baseline serum eosinophil counts. Response to omalizumab was assessed by three criteria: physician evaluation, reduction of ≥ 40% in annual exacerbation rate (AER) or a combination of both. The observed effectiveness was similar in both eosinophil groups, and the authors suggest that omalizumab effectiveness is similar in "high" and "low" eosinophil subgroups.[61] This contrasts with the before-mentioned PROSPERO trial, in which patients with high baseline serum eosinophil counts were more likely to be ACT responders.[54] Also, a post-hoc analysis of biomarkers in the EXTRA study suggests more benefit for patients with higher levels of baseline blood eosinophils. In this study the authors explored the potential of type 2 inflammatory biomarkers (blood eosinophils, FeNO and serum

Table 2
Overview of outcome measures and treatment effects in phase III biological trials in severe asthma.

Biologic		Response outcomes	
Study	N total (Treated – Placebo)	Primary outcome	Results Associations (treatment vs placebo)
Omalizumab			
Busse 2001[40]	525 (268–257)	Number of asthma exacerbations after 16 wks (part I) and after ICS reduction phase of 12 wks (part II)	**Exacerbations per patient, mean:** Part I: 0.28 vs 0.54p < 0.01 Part II: 0.39 vs 0.66p < 0.01
Solèr 2001[41]	546 (274–272)	Asthma exacerbation rate after 16 wks (part I) and after ICS reduction phase of 12 wks (part II)	**Exacerbations per patient , mean (95% CI):** Part I: 0.28 (0.15–0.41) vs 0.66 (0.49–0.83) Part II: 0.36 (0.24–0.48) vs 0.75 (0.58–0.92)
Mepolizumab			
Bel 2014[42]	135 (69–66)	Chance on a reduction in OCS dose category at 24 wks	**OCS reduction chance, OR (95% CI):** 2.39 (1.25–4.56) p < 0.01
Ortega 2014[43]	576 (385–191)	Asthma exacerbation rate at 32 wks	**Exacerbation rate, Reduction rate (95% CI)** 75 mg IV: 47% (28–60) p < 0.01100 mg SC: 53% (36–65) p < 0.01
Reslizumab			
Castro 2015[44]	953 (477–476)	Asthma exacerbation rate at 52 wks2 studies enclosed	**Exacerbation rate,** RR **(95% CI):** Study 1: 0.50 (0.37–0.67) p < 0.01 Study 2: 0.41 (0.28–0.59) p < 0.01
Bjermer 2016[45]	315 (210–105)	Change in pre-bronchodilator FEV1 at 16 wks	**FEV1 change, LSM-TD (95% CI):** 0.160 (0.060–0.259) p < 0.01
Benralizumab			
Bleecker 2016[46]	1205 (798–407)	Asthma exacerbation rate at 48 wks	**Exacerbation rate, RR (95% CI):** Q4W: 0.55 (0.42–0.71) p < 0.01 Q8W 0.49 (0.37–0.64) p < 0.01
FitzGerald 2016[47]	1306 (866–400)	Asthma exacerbation rate at 56 wks	**Exacerbation rate, RR (95% CI):** Q4W: 0.64 (0.49–0.85) p < 0.01 Q8W 0.72 (0.54–0.95) p = 0.02
Nair 2017[48]	220 (145–75)	Chance on a reduction in OCS dose category at 28 wks	**OCS reduction chance, OR (95% CI):** Q4W: 4.09 (2.22–7.57) p < 0.01 Q8W: 4.12 (2.22–7.63) p < 0.01
Dupilumab			
Castro 2018[49]	1902 (1264–638)	1. Asthma exacerbation rate at 52 wks,2. Pre-bronchodilator change in FEV1 at 12 wks	**Exacerbation rate, Relative Risk (95% CI):** 200 mg dose: 0.52 (0.41–0.66) 300 mg dose: 0.54 (0.43–0.68) **FEV1 change (L),** LSM-TD (95% CI): 200 mg dose: 0.14 (0.08–0.19) p < 0.01 300 mg dose: 0.13 (0.08–0.18) p < 0.01
Rabe 2018[50]	210 (103–107)	Percentage OCS dose reduction at 24 wks	**OCS change, LSM ± SE:** −70.1% ± 4.9% vs −41.9% ± 4.6% p < 0.01

Listed are the studies, number of participating patients and comparator arms, primary outcomes, and reported associations (treatment vs placebo). Abbreviations: CI = confidence interval, FEV1 = forced expiratory volume in 1 s, ICS = inhaled corticosteroids, IV = intravenous dose, LSM-TD = least squares mean treatment difference, Q4W = treated every 4 weeks, Q8W = treated every 8 weeks, OCS = oral corticosteroids, OR = odds ratio, RR = rate ratio, SC = subcutaneous dose, SD = standard deviation, SE = standard error.

periostin) to serve as baseline predictors of therapeutic benefit of omalizumab treatment. Patients were divided into baseline low- and high-biomarker subgroups with cutoff values: FeNO < 19.5 ppb or ≥ 19.5 ppb, eosinophils < 260 cells/μL or ≥ 260 cells/μL and periostin < 50 ng/mL or ≥ 50 ng/mL. It turned out that the reduction in exacerbations was larger in all three high baseline biomarker subgroups as compared with the low biomarker subgroups, indicating that these patients may achieve greater benefit from omalizumab therapy.[62] In addition, FEV1 normalization after a year of omalizumab therapy was found to be associated with higher baseline values of FeNO and serum eosinophil count.[63] Though the evidence may not be fully consistent, the Global Initiative for Asthma added the criteria FeNO ≥ 20 ppb or serum eosinophils ≥ 260 cells/μL as factors that may predict good asthma response to anti-IgE.[64] Interestingly, from a recent pilot study, the authors report that omalizumab is possibly inadequate to control sputum eosinophilia, and therefore may not have a steroid-sparing effect, especially in those maintained on oral corticosteroids daily.[65]

Total serum IgE-level is a sum of active and inactive (omalizumab-bound) IgE. After initiating omalizumab treatment, the serum IgE-level

Table 3
Overview of studies on prediction of response to biological treatment in severe asthma.

Study	N Total (Treated–Placebo)	Predicting variable(s)	Response outcome	Conclusion	Association
Omalizumab					
[54] Casale 2019	737	Gender Pos. allergen specific IgE Serum eosinophilsACT	Responder: at 48 weeks 1 AER reduction ≥ 50% or 2 ACT improvement to ≥ 20 or 3 point ACT improvement or 3 FEV1 improvement ≥ 120 mL	Predictive	**Odds of being a responder, OR (95% CI)** To criteria 1, 2 and 3:Males: 0.49 (0.28–0.86) p = 0.01; Spec. IgE: 4.36 (1.38–16.92) p = 0.02 To criterion 2: Eosinophils ≥ 300 cells/μL: 1.65 (1.10–2.51) p = 0.02 To criterion 3: ACT ≥ 20: 0.49 (0.25–0.91) p = 0.03
[57] Gibson 2016	180	ACQ-5Age	Responder at 26 weeks: ACQ-5 improvement ≥ 0.5	Predictive	**Coefficient (SE):** ACQ ≥ 2.0: −142.24 (44.29) p < 0.01 Age: 1.52 (0.77) p = 0.05
[61] Humbert 2018	723	Serum eosinophils	Responder: Combined: AER reduction ≥ 40% + GETE at 4–6 months	Not predictive	**Responders, N, n(%) (95% CI)** ≥300 cells/μL: 220 (58.4) (53.3–63.4) < 300 cells/μL: 201 (58.1) (52.7–63.4)
[62] Hanania 2013	850 (427–423)	FeNO Serum eosinophils Periostin	Exacerbation reduction at 48 weeks vs placebo	High subgroups predictive	**Exacerbation: Percentage reduction vs placebo (95% CI)** FeNO: ≥19.5: 53% (37–70) p = 0.001, < 19.5: 16% (–32–46) p = 0.45 Serum eosinophils: ≥260/μL: 32% (11–48) p = 0.005, < 260/μL: 9% (-24–34) p = 0.54 Periostin: ≥50 ng/mL: 30% (-2–51) p = 0.07, < 50 ng/mL: 3% (-43–32) p = 0.94
[72] Bousquet 2007	195 (118–77)	Physician's overall assessment at 16 weeks	Responder: at 16 weeks AER vs placebo	Predictive	**Responders vs non-responders**, AE rate vs placebo (SD): 0.6 (1.31) vs 2.6 (6.39)
Mepolizumab					
[74] Pavord 2012	621 (462–159)	Serum eosinophils AER in the previous yearFeNO	AER vs placebo	Eosinophils and exacerbations predictive	**AER: RR vs placebo (95% CI)** Serum eosinophils: ≤150 cells/μL: 0.92 (0.58–1.45); > 150 cells/μL - ≤300 cells/μL: 0.45 (0.25–0.80); > 300 cells/μL - ≤500 cells/μL: 0.69 (0.43–1.09); > 500 cells/μL: 0.27 (0.19–0.39) Previous exacerbations: 2: 0.87 (0.59–1.30); 3: 0.43 (0.29–0.65); ≥4: 0.36 (0.25–0.54) FeNO: < 50 ppb: 0.63 (0.47–0.84); FeNO ≥ 50 ppb: 0.43 (0.30–0.63)
[78] Albers 2019	936 (468–468)	BMI	AER vs placebo	Not predictive	**AER: RR vs placebo (95% CI)** BMI: ≤25 kg/m^2 0.38 (0.26–0.56); > 25–30 kg/m^2 0.45 (0.32–0.63); > 30 kg/m^2 0.51 (0.35–0.73)
[80] Ortega 2016	1192 (846–346)	Serum eosinophils	AER vs placebo FEV1 vs placebo ACQ-5 vs placebo	More AER reduction in increasing eosinophil subgroups	**AER: RR vs placebo (95% CI)** Serum eosinophils: ≥150 cells/μL: 0.48 (0.39–0.58); ≥300 cells/μL: 0.41 (0.33–0.51) ≥400 cells/μL: 0.34 (0.27–0.44); ≥500 cells/μL: 0.30 (0.23–0.40) **Change in FEV1 (mL) (95% CI)** Serum eosinophils: ≥150 cells/μL: 64 (1–127); ≥300 cells/μL: 68 (-10–146); ≥500 cells/μL: 106 (-2–214) **Change in ACQ-5 (95% CI)**

(*continued on next page*)

Table 3 (*continued*)

Study	N Total (Treated–Placebo)	Predicting variable(s)	Response outcome	Conclusion	Association
					Serum eosinophils: ≥150 cells/μL: −0.35 (-0.49- −0.20); ≥300 cells/μL: −0.49 (-0.67- −0.31); ≥500 cells/μL:- 0.61 (-0.85- −0.37)
[81] Albers 2019	936 (468–468)	Serum eosinophils	AER vs placebo	More AER reduction in increasing eosinophil subgroups	**AER: RR vs placebo (95% CI)** Serum eosinophils: < 150 cells/μL: 0.55 (0.34–0.89); ≥150 cells/μL: 0.43 (0.34–0.54); ≥300 cells/μL: 0.36 (0.28–0.48); ≥400 cells/μL: 0.30 (0.22–0.41); ≥500 cells/μL: 0.29 (0.20–0.41); ≥750 cells/μL: 0.15 (0.08–0.29
[87] Condreay 2017	820	Subset of asthma related genetic markersGWAS	Exacerbation rate Change in eosinophil countChange in IgE level	Not predictive	N/A
[84] Shrimanker 2019	606 (455–151)	Combination FeNO and serum eosinophils	AER vs placebo	FeNO not associated with AER, blood eosinophils is associated	**AER: RR (95% CI)** Serum eosinophils/FeNO: < 150 cells/μL/ < 30 ppb: 0.86 (0.47–1.57); < 150 cells/μL/≥ 30 ppb: 0.94 (0.37–2.40)≥150 cells/μL/ < 30 ppb: 0.64 (0.42–0.99); ≥150 cells/μL/≥30 ppb: 0.38 (0.27–0.53)
[88] Gunsoy 2018	263 (120–126)	At 16 weeks: Reduction in eosinophils PRTRACQ-5 improvement FEV1 improvement No change or reduction in exacerbations	AER vs placebo	Not predictive	**DREAM study reported AER: Placebo adjusted rate ratio (95% CI)** Reduction from baseline eosinophils: ≥20%: 0.73 (0.20–2.67); ≥40%: 0.84 (0.27–2.64) ≥60%: 0.90 (0.35–2.33); ≥80%: 0.66 (0.25–1.69) Physician-rated treatment responseModerate/significant improvement: 0.92 (0.44–1.91); Any improvement: 0.77 (0.36–1.61) ACQ-5: 0.69 (0.34–1.40) FEV1 ≥ 10%: 0.96 (1.46–2.01) No change or reduction in exacerbations: 0.60 (0.28–1.29)
Reslizumab					
[44] Castro 2015	953 (477–476)	AER in the last year	AER vs placebo	Stronger effect with more exacerbations	**AER: RR vs placebo (95% CI)** AER in last year: All: 0.46 (0.37–0.58); 1: 0.68 (0.49–0.95); 2: 0.44 (0.28–0.69) 3: 0.39 (0.21–0.70); ≥4: 0.36 (0.22–0.58)
[89] Brusselle 2017	931 (465–446)	Age of onset	AER vs placebo FEV1 vs placebo	Greater improvements with higher age of onset	**AER: RR vs placebo (95% CI)** Onset: ≥40 years: 0.25 (0.16–0.40); < 40 years: 0.58 (0.44–0.76) **FEV1 (mL) change from baseline (95% CI)** Onset: ≥40 years: 167 (89–245); < 40 years: 88 (34–142)
[91] Nair 2019	953 (477–476)	AER in the last year Age, gender, race, BMI, age of onset, atopic status, chronic rhinosinusitis with nasal polyposis	AER vs placebo	Stronger effect with more exacerbations, other variables not predictive	**AER: risk reduction vs placebo(95% CI)** AER in last year: ≥2: 77.5% (58%-88%) 1:15.2% (-150.5%-71.2%) (p = 0.028) Other variables N/A
[92] Corren 2016	492 (395–97)	Serum eosinophils	At 16 weeks: Change in FEV1 vs placebo ACQ-7 vs placebo	No effect in low-eosinophil subgroups	**Treatment effect FEV1 (L) change versus placebo (95% CI):** Eosinophils < 400 cells/μL: 0.03 (-0.07–0.14) Eosinophils ≥ 400 cells/μL: 0.27 (0.01–0.53) **Treatment effect ACQ-7 change versus placebo (95% CI):** Eosinophils < 400 cells/μL: −0.12 (-0.33–0.087) Eosinophils ≥ 400 cells/μL: −0.49 (-1.01–0.03)

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Table 3 (*continued*)

Study	N Total (Treated–Placebo)	Predicting variable(s)	Response outcome	Conclusion	Association
[93] Bateman 2019	321	Predictive model using: changes in ACQ, AQLQ, and FEV1 at 16 weeks, asthma exacerbations (previous year and in first 16 weeks)	Responder at 52 weeks:Combination of exacerbation rate and FEV1 improvement, ACQ-6 and AQLQ improvement at 52 weeks	Predictive for response, not for non-response	**Model performance:** PPV: 89.9% (95% CI, 87.1–92.1%) NPV: 50.0% (95% CI, 33.7–66.3%)
Benralizumab					
[96] FitzGerald 2018	2295 (1518–777)	Serum eosinophils AER in the previous year	AER vs placebo	Enhanced efficacy in higher eosinophil and previous AER subgroups	**8 weekly benralizumabAER: RR vs placebo (95% CI)** Eosinophils: ≥0 cells/μL: 0.64 (0.55–0.75); ≥150 cells/μL: 0.63 (0.53–0.74); ≥300 cells/μL: 0.57 (0.47–0.69); ≥450 cells/μL: 0.50 (0.38–0.64) 2 AER in previous year + eosinophils ≥ 300 cells/μL: 0.73 (0.55–0.95)≥ 3 AER in previous year + eosinophils ≥ 300 cells/μL: 0.45 (0.34–0.60)
[97] Bleecker 2018	2295 (1518–777)	OCS-useNasal polyposis FVCAER in the previous year Age at diagnosis	AER vs placebo FEV1 improvement vs placebo	Predictors were associated with response	**AER: RR vs placebo (95% CI)** OCS-use: 0.42 (0.29–0.60); No OCS-use: 0.69 (0.58–0.82) Nasal polyposis: 0.50 (0.35–0.72); no nasal polyposis : 0.68 (0.57–0.81) FVC < 65% pred.: 0.53 (0.39–0.71); FVC ≥ 65%pred: 0.69 (0.58–0.83)≥3 AER: 0.54 (0.43–0.67); 2 AER: 0.74 (0.60–0.90) Age at diagnosis ≥ 18 yrs: 0.59(0.49–0.71); Age at diagnosis < 18 yrs: 0.79 (0.61–1.02) **FEV1 (L) improvement: LS (95% CI)** OCS-use: 0.19 (0.06–0.31) No OCS-use: 0.08 (0.02–0.13)Nasal polyposis:: 0.29(0.17–0.41); No nasal polyposis: 0.06 (0.01–0.011) FVC < 65% pred.: 0.21 (0.10–0.31); FVC ≥ 65%pred: 0.06 (0.01–0.12) ≥3 AER: 0.17 (0.09–0.26); 2 AER: 0.05 (-0.01–0.11) Age at diagnosis ≥ 18 yrs: 0.14 (0.09–0.20); Age at diagnosis < 18 yrs: −0.01 (-0.11–0.18)
[98] Chipps 2018	2295 (1518–777)	Serum IgEAtopic status	AER vs placebo FEV1 improvement vs placebo	No difference found	**8 weekly benralizumabAER: RR vs placebo(95% CI)** IgE ≥ 150 KU/L: 0.58 (0.45–0.75); IgE < 150 KU/L: 0.57 (0.41–0.78) Atopy: 0.60 (0.47–0.77); No atopy: 0.54 (0.39–0.74) **FEV1 (L) improvement: LS mean difference vs placebo(95% CI)** IgE ≥ 150 KU/L: 0.123 (0.041–0.205); IgE < 150 KU/L: 0.138 (0.044–0.233) Atopy: 0.114 (0.033–0.194); No atopy: 0.181 (0.085–0.278)
Dupilumab					
[49] Castro 2018	1902 (1264–638)	Serum eosinophils FeNO	AER vs placebo FEV1 improvement at 12 weeks vs placebo	Greater efficacy in higher eosinophil and FeNO subgroups	**Dupilumab 300 mg every 2 weeks** **AER: RR vs placebo (95% CI)** Serum eosinophils: ≥300 cells/μL: 0.33 (0.23–0.45); ≥150 - < 300 cells/μL: 0.56 (0.35–0.89); < 150 cells/μL: 1.15 (0.75–1.77)FeNO (ppb) RR (95% CI): ≥50: 0.31 (0.19–0.49); ≥25 - < 50: 0.44 (0.28–0.69); < 25: 0.79 (0.57–1.10) **FEV1 (L) LS mean diff. vs placebo (95% CI)** Serum eosinophils: ≥300 cells/μL: 0.24 (0.16–0.32; ≥150 - < 300 cells/μL: 0.00(-0.10, 0.10); < 150 cells/μL: 0.09 (-0.01–0.18) FeNO (ppb) RR (95% CI) ≥50: 0.39 (0.26–0.52); ≥25 - < 50: 0.12 (0.03–0.21); < 25: 0.03 (-0.04–0.10)

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Table 3 (*continued*)

Study	N Total (Treated–Placebo)	Predicting variable(s)	Response outcome	Conclusion	Association
[50] Rabe 2018	210 (103–107)	Serum eosinophils	OCS reduction at 24 weeks vs placebo	Greater efficacy in higher eosinophil subgroups	**OCS reduction LS mean difference (95% CI)** Serum eosinophils: ≥300 cells/μL: −36.8 (-54.7- −18.9); < 300 cells/μL: −21.3 (-38.8- −3.9) ≥150 cells/μL: −29.4 (-43.1- −15.7); < 150 cells/μL: −26.9 (-54.5–0.7)
[100] Corren 2019	465 (307 – 158)	AER in the previous yearFEV1	ACQ AQLQ	Greater efficacy with more exacerbations an lower FEV1	**Dupilumab 300 mg every 2 weeks** **ACQ LS mean change (± SE)** AER in previous year: ≤1: −1.12 (0.10) : > 1: −1.70 (0.11) p < 0.01FEV1 (L): ≤1.75: −1.50 (0.11); > 1.75: −1.44 (0.11) p = 0.10 **AQLQ LS mean change (± SE)** AER in previous year: ≤1: 0.92 (0.11); > 1: 1.51 (0.12) p < 0.01 FEV1 (L): ≤1.75: 1.31 (0.12); > 1.75: 1.19 (0.12) p < 0.05[95]
[101] Corren 2019	1902 (1264–638)	Allergic asthma	AER vs placebo FEV1 improvement at 12 weeks vs placebo ACQ improvement at 24 weeks vs placebo	Outcomes improved regardless of allergic asthma	**Dupilumab 300 mg every 2 weeks** **AER reduction vs placebo % (95% CI):** With allergies:36.9% (13.4–54.0); Without allergies: 60.0% (42.7–72.1) **FEV1 improvement LS mean (L) (95% CI)** With allergies: 0.16 (0.09–0.23); Without allergies: 0.09 (0.01–0.16) **ACQ LS mean change (95%** CI) With allergies:-0.26 (-0.44–0.08); Without allergies: −0.08 (-0.29–0.12) [95]
[103] Yang 2019	2992 (N/A)	FeNO	AER vs placebo FEV1 at 12 weeks vs placebo	Greater efficacy in higher FeNO subgroups	**AER, mean difference vs placebo, rate estimate (95% CI)** Baseline FeNO: ≥ 50 ppb: −0.78 (-1.08- −0.47); ≥25 ppb < 50 ppb −0.62 (-0.88- −0.36) < 25 ppb: −0.18 (-0.34- −0.01) **FEV1 at 12 weeks, mean difference vs placebo, change from baseline (95% CI)** Baseline FeNO: ≥ 50 ppb: 0.35 (0.26–0.43); ≥25 ppb < 50 ppb: 0.15 (0.09–0.22) < 25 ppb: 0.07 (-0.01–0.14)

Presented are studies with ≥ 100 participants. Listed are the studies, number of participating patients and comparator arms, predicting variables, outcome measures, conclusions, and reported associations. Predicting parameters are baseline (status at biologic initiation) if not specified otherwise. Abbreviations: ACQ = asthma control questionnaire, ACT = asthma control test, AER = annualized exacerbation rate, AQLQ = asthma-related quality of life questionnaire, BMI = body mass index, CI = confidence interval, FeNO = Nitric Oxide in exhaled breath, FEV1 = forced exhaled volume in 1 s, FVC = forced vital capacity, GETE = global evaluation of treatment effectiveness, GWAS = genome wide association study, IgE = Immunoglobulin E, N/A = not available, NPV = negative predictive value, OCS = oral corticosteroid, OR = odds ratio, PPV = positive predictive value, PRTR = physician-rated treatment response, Q8W = treated every 8 weeks, RR = rate ratio, SD = standard deviation, SE = standard error, TARC = thymus and activation regulated cytokine.

increases due to the binding of omalizumab to IgE, increasing the IgE half-life. Thus, measuring the total IgE-level is not an applicable tool to measure therapy-response while receiving omalizumab. The diagnostic value of monitoring free IgE-levels in the omalizumab response-evaluation has been studied, but only in small studies and results are indecisive.[66,67]

The aforementioned potential of periostin as predictive biomarker is further supported by a small prospective study in 30 patients who had been treated with omalizumab for at least 1 year. This study showed an association between high baseline levels of periostin and omalizumab induced absence of exacerbations and improved AQLQ-scores.[67] Currently, periostin assays are commercially available, but used for research purposes only.

Exploratory biomarkers

Several small studies investigated the predictive capabilities of different explorative biomarkers and found that patients responding to omalizumab had significant higher baseline levels of serum IL-12 and sputum IL-13.[58,68,69] In addition, associations with markers of airway remodeling and physician assessment scores were found for galectin-3 levels in bronchial tissue, and degree of syk expression with associated IgE-mediated histamine release, respectively.[70,71] Though very interesting and sometimes promising, these results are not yet applicable in common care and future studies are awaited to test their predictive capacity.

Early evaluation parameters to predict long term omalizumab response

In addition to baseline characteristics, evaluation parameters after short-term treatment might have added value to predict long-term treatment response. A post-hoc analysis of the INNOVATE study deemed the physician's overall assessment after 16 weeks of therapy predictive for annual exacerbation risk.[72] This finding was confirmed in a pooled analysis of seven omalizumab RCTs, whereas no other individual parameters, nor baseline serum IgE level predicted long-term response.[72] As a result, the 16 week evaluation moment is included in the Xolair® Summary of Product Characteristics to decide whether to continue omalizumab therapy or not.[73].

Conclusions omalizumab

Baseline characteristics predicting omalizumab benefit include a history of frequent exacerbations, poor asthma control and the presence of a positive allergen-specific IgE test. Higher levels of blood eosinophils or FeNO further add to the expectation of better outcomes. The relative early assessment of treatment response at 16 weeks is already adopted in clinical practice and shown to be helpful in the prediction of future benefit.

3.2. Anti-IL-5 biological treatment

In the last years, three biologics targeting IL-5 were registered in the EU and USA for the treatment of severe eosinophilic asthma. Since these biologics are relatively new, there are no large prospective trials primarily aimed at prediction of response for these drugs yet.

Mepolizumab: baseline characteristics to predict medium and long term treatment response

Mepolizumab was the first registered anti-IL-5 biologic (2014) and is given subcutaneous (SC) every 4 weeks in a fixed dose of 100 mg. Since mepolizumab was the first available anti-IL-5 biologic, relatively much therapeutic experience has been gained. In selecting treatment eligible patients, an eosinophil cut-off value of ≥ 150 cells/μL is utilized.[35]

Clinical and functional parameters. Only a few studies explored baseline clinical or functional parameters as potentially predictors of response. In the Dose Ranging Efficacy And safety with Mepolizumab (DREAM) phase 2 study, an exploratory modelling of baseline characteristics indicated that efficacy of mepolizumab increases with increasing baseline eosinophil counts and numbers of exacerbations in the previous year, but not with atopic status, gender, weight, or FEV1.[74] A retrospective review of 52 patients with OCS dependent asthma found 73% of the patients to be responder (≥ 50% reduction in OCS dose by 12 months). At baseline, responders had significantly lower daily OCS dose, better asthma control, were more often non-atopic and tended to have a lower body mass index (BMI).[75] Another small study with 32/42 responders, found no baseline parameters (gender, BMI, smoking history, allergies, and blood eosinophil levels) that predicted treatment response.[76]. Two meta-analyses combining the MENSA and MUSCA RCT data investigated the relationship between baseline percentage predicted FEV1 or BMI, and mepolizumab induced reduction in exacerbation rate, but no association was found.[77,78] This suggests that baseline airway obstruction nor BMI are factors that predict treatment response, in line with the covariate modelling analysis in DREAM.[74]

Inflammatory parameters. Several other studies confirmed the increased efficacy of mepolizumab with increasing baseline blood eosinophil counts.[43,74,79,80] Large post-hoc analyses of data from the mepolizumab RCTs (DREAM, MENSA, MUSCA) revealed similar results: there is a close positive relationship between baseline blood eosinophil count and clinical efficacy of mepolizumab, consistently regarding exacerbation reduction, and with less conclusive evidence considering improvement in FEV1 and asthma control.[78,80,81] At < 150 cells/μL, predicted efficacy was reduced, particularly for the DREAM study. Interestingly, blood eosinophil counts appear to be a better predictor of response than sputum eosinophil counts.[74]

In addition to eosinophils, other biomarkers have been investigated. In a proof of concept trial, FeNO levels were not responding to mepolizumab treatment, neither were baseline FeNO levels predictive of response.[82] This was confirmed in the DREAM trial were exacerbation rate reduction was similar in the high (≥ 50 ppb) and low (< 50 ppb) FeNO subgroups [74], suggesting that FeNO is not responsive to IL-5 modulation, but might be more relevant in different aspects of the type 2 inflammatory process.[83] Yet, when both blood eosinophils and FeNO levels are increased, mepolizumab seems to be most effective. A post-hoc analysis of the DREAM trial divided 606 participants in four groups: high or low peripheral blood eosinophils combined with high or low FeNO. It was found that patients in the high serum eosinophil subgroups had a reduced exacerbation rate compared to the low eosinophil subgroup, regardless of having high or low FeNO. However, patients with the combination of high FeNO and high serum eosinophil counts had the most benefit of mepolizumab treatment.[84] Though caution is needed when interpreting such post-hoc analyses, this suggests that a combined biomarker profile might have greater prognostic value.

Exploratory biomarkers. Assessment of serum IL-5 is not commercially available for diagnostic means and is therefore not extensively investigated. A small study in 5 patients found that non-responders, according to OCS-use and exacerbation frequency, had an increase in IL-5 concentrations at 12 weeks, but these results need to be confirmed in larger studies.[85] Siglec-8, a transmembrane receptor on eosinophils, may act as a surrogate parameter, since it is regulated by IL-5. In a study in 12 patients, it was found that patients with low serum Siglec-8 had a trend towards better FEV1 and AQLQ improvements, but no correlation with serum eosinophil counts was found.[86]

An emerging aspect of modern health-care is the utilization of a patient's genetic profile in medical decision making. A post-hoc analysis of the DREAM and MENSA trial data tested the association between asthma-specific genetic markers and mepolizumab efficacy in 820 patients, but found no association.[87]

Early evaluation parameters to predict long term mepolizumab response

Currently there is only 1 study available using early evaluation parameters. This post-hoc analysis assessed to what extent clinical markers and biomarkers measured 16 weeks after treatment initiation might predict long-term treatment response based on exacerbation reduction, and could be used as a continuation rule. The authors analyzed data from the DREAM and MENSA trials and found only a marginal influence of changes in blood eosinophils after 16 weeks of treatment. No evidence was found for a continuation rule based on physician-rated response, ACQ-5 score, or lung function.[88]

Reslizumab: Baseline characteristics to predict medium and long term treatment response

Reslizumab was the second available anti-IL-5 biologic, registered in 2017 for the treatment of severe eosinophilic asthma. As opposed to mepolizumab, reslizumab is administered intravenously every 4 weeks and is dosed based on bodyweight (3 mg/kg). The intravenous administration has to be performed in the clinic, warranting the patient adherence. The dosing based on bodyweight leads to a personalized treatment. In selecting treatment eligible patients, an eosinophil cut-off value of ≥ 400 cells/μL is utilized.[36]

Clinical and functional parameters. Only a few studies address the topic of predicting reslizumab response using baseline clinical characteristics. Exploratory analyses in phase 3 trials suggested that previous exacerbations exerted a strong effect on the reduction of clinical asthma exacerbation rate by reslizumab.[44] In a post-hoc analysis using phase 3 trial data, reslizumab efficacy was compared in 658 patients with early-onset asthma versus 273 with late-onset asthma (cut-off 40 years). Though beneficial in both groups, larger reslizumab induced reductions in asthma exacerbations and improvements in lung function were found in patients with late-onset asthma.[89] This is in line with results from a pooled analysis of 477 patients from two phase 3 reslizumab trials assessing characteristics of non–, moderate-, high-, and super-responders. Comparing non-responders and super-responders, super-responders tended to have later age of onset, as well as lower BMI, higher baseline ACQ and a history of nasal polyps, with no significant differences in age, gender, baseline lung function, or baseline medications.[90] The same trials were used in a post-hoc analysis using patients on daily OCS. To determine predictors of asthma exacerbation response, several parameters were used: age, gender, race, BMI, weight, number of exacerbations in the previous year, late-onset asthma, atopic status, chronic rhinosinusitis with nasal polyps, and blood eosinophil count. The only characteristic associated with reduced exacerbation risk with reslizumab, was having 2 or more versus 1 clinical asthma exacerbation in the previous 12 months.[91]

Inflammatory parameters. To assess whether baseline serum eosinophil count has an effect on reslizumab outcomes, a study was conducted in a population unselected for baseline blood eosinophil level, in contrast to the previous reslizumab RCTs that used a cut-off value of ≥ 400 eosinophil cells/μL to include patients. The resuIts showed that reslizumab did not meaningfully improve asthma outcomes, including both lung function and measures of symptom control, in patients with blood eosinophil counts < 400 cells/μL.[92]

Early evaluation parameters to predict long-term reslizumab response

A large study was conducted to predict long-term response and non-response in patients after 16 weeks of reslizumab treatment. The authors used an algorithm they developed based on clinical indicators from pivotal clinical trials, including change from baseline to 16 weeks in ACQ and AQLQ scores and FEV1, and number of asthma exacerbations. The algorithm was evaluated for its ability to predict response at 52 weeks, based on AER, FEV1 improvement, ACQ-6 improvement or AQLQ-improvement. The algorithm had 95.4–95.5% sensitivity and 40.6–54.1% specificity, and was successful at predicting response at 52 weeks, but failed regarding the potentially more important prediction of long-term non-responders.[93]. So unfortunately the algorithm might add little to routine practice, as it will not change the need for a 12-month trial of treatment, and this would ideally be the outcome of such a prediction model.[94]

Benralizumab: baseline characteristics to predict medium and long term treatment response

Benralizumab was registered in the EU and USA in 2017 for the treatment of severe eosinophilic asthma. Benralizumab is given in 30 mg SC injections, initially every 4 weeks and after three gifts every 8 weeks. The dosing interval of 8 weeks is the longest of the five biologics, which is an advantage of benralizumab therapy. In selecting treatment eligible patients, an eosinophil cut-off value of ≥ 150 cells/μL is utilized.[95]

Clinical and functional parameters. For benralizumab, the impact of baseline factors on treatment efficacy has been investigated in 3 post-hoc analyses using data from benralizumab phase 3 trials (SIROCCO and CALIMA).[96–98] These studies contained a total of 2295 patients: 756 received 4-weekly 30 mg benralizumab (Q4W), 762 8-weekly 30 mg benralizumab (Q8W) and 777 placebo.

Several clinical and functional baseline factors that might influence benralizumab efficacy were evaluated, including OCS use, nasal polyposis, pre-bronchodilator forced vital capacity (FVC), prior year exacerbations and age at diagnosis. Efficacy outcomes included AER and change in pre-bronchodilator FEV1 at treatment end relative to placebo. Patients with any of the abovementioned factors had greater reduction in AER, and more improvement in lung function with benralizumab Q8W versus placebo compared with the efficacy in the overall population and those with blood eosinophil counts ≥ 300 cells/μL. For the overall population, OCS use and nasal polyposis had the greatest influence on improvement of AER, whereas nasal polyposis and pre-bronchodilator FVC < 65% of predicted had the greatest influence on increasing FEV1.[97] In another analysis, benralizumab treatment was found to decrease exacerbations and improve lung function regardless of serum IgE concentrations and atopic status.[98]

Inflammatory parameters. When focusing on the impact of different baseline blood eosinophil thresholds (≥ 0, ≥ 150, ≥ 300, or ≥ 450 cells/μL) and number of exacerbations (two vs three or more) in the previous year, the Fitzgerald study showed that the degree of improvement in AER increased with increasing baseline blood eosinophil counts, and enhanced efficacy was observed for patients with increased blood eosinophils combined with a history of three or more exacerbations per year.[96] Though efficacy was reported in the patients with eosinophil levels ≥ 0 cells/μL, the absence of significant effect in the subgroup of patients with eosinophils < 150 cells/μL requires restraint with regard to treatment with benralizumab in the patients with low eosinophil numbers.

To our knowledge, there is no study available using evaluation parameters after some months of treatment to assess longer-term benralizumab benefit.

Conclusion anti-IL-5 biologics

A history of frequent exacerbations and higher levels of blood eosinophils are consistently identified in the different IL-5 targeting trials as baseline characteristics that predict treatment response regarding exacerbation reduction and lung function improvement. The presence of late-onset asthma, OCS dependency, impaired lung function and nasal polyposis might further increase the chance of good response. So far, the added value of early evaluation parameters to predict future treatment response is still debatable.

3.3. Dupilumab: baseline characteristics to predict medium and long term treatment response

Dupilumab is an anti-IL-4 receptor antagonist, preventing the function of both IL-4 and IL-13 in the type 2 inflammation cascade (Fig. 1). Dupilumab was first registered in the treatment of moderate-to-severe atopic dermatitis. In 2018 the indication for severe eosinophilic asthma was added. Dupilumab is given in 200 mg or 300 mg SC injections every 2 weeks after a 400 mg or 600 mg loading dose, based on OCS use or concomitant atopic dermatitis. Recently, the FDA approved dupilumab for treatment of chronic rhinosinusitis with nasal polyposis. [99] This relatively large range of indications, some of which are common comorbidities in patients with severe asthma, is a major advantage of dupilumab.

Clinical and functional parameters. Since dupilumab has only recently been registered for use in severe asthma, studies on clinical or functional characteristics predicting response are limited. In a post-hoc analysis of a phase 2b trial, patients with a history of $>$ 1 exacerbation in the prior year or baseline FEV1 $\leq$ 1.75 L, showed a better response to dupilumab in asthma control and quality of life scores.[100]

Inflammatory parameters. A post-hoc analysis of the phase 3 study LIBERTY ASTHMA QUEST, found that dupilumab reduced severe exacerbation rates, improved FEV1 and asthma control, and suppressed type 2 inflammatory biomarkers in both allergic and non-allergic asthma.[101] Reductions in severe exacerbation rates and improvement in FEV1 were greater in patients with higher baseline levels of type 2 inflammatory biomarkers. These findings are consistent with previous dupilumab studies, showing that dupilumab treatment results in a lower AER and a higher FEV1 across the whole spectrum of baseline blood eosinophil counts, however these benefits are more pronounced in patients with higher levels of baseline blood eosinophils or FeNO.[49,50,102,103]

Explorative biomarkers. In addition to blood eosinophils and FeNO, other type 2 associated biomarkers have been explored, such as serum IgE, thymus and activation regulated chemokine, and eotaxin-3, but so far none defined a subpopulation more responsive to treatment. [49,103,104]

Currently, there is no study available using evaluation parameters after some months of treatment to assess longer-term dupilumab benefit in severe asthma.

Conclusion dupilumab

Baseline characteristics predicting dupilumab benefit are still far from clear and mainly concern inflammatory parameters. Though efficacy is shown regardless of baseline eosinophil levels, the magnitude of response seems to increase with increasing levels of baseline blood eosinophils or FeNO.

3.4. Exclusion of the use of biologics in severe asthma

This manuscript focuses on parameters for the initiation of MABs. However, there are some reasons for excluding the use of biologics in severe asthma. Obviously, failing to meet the inclusion criteria is the main reason for not starting a biologic. The main inclusion criteria are uncontrolled asthma despite optimized inhalation therapy and evidence of type 2 inflammation.[64] For the individual biologics, serum eosinophils $<$ 150 cells/μL excludes the use of anti-IL-5 biologics. Pre-treatment serum IgE $<$ 30 IU/L or $>$ 1300 IU/L falls outside the omalizumab dosing table and excludes the use of omalizumab. Dupilumab is applicable for all patients with evident type 2 inflammation. Furthermore, the biologics are contraindicated in patients with hypersensitivity to the biologic and patients with a helminth infection. The components of type 2 inflammation (IgE, IL-4, IL-5, IL-13 and eosinophils) are involved in the immune response against helminths. Interfering with this immune response using biologics, while a helminth infection is present, might lead to life-threatening infections.[105] Using biologics during pregnancy is currently contra-indicated due to the lack of experience in pregnant women.

4. Future perspectives

New perspectives in response prediction of the MABs used in severe asthma may present themselves in the near future. Four possible aspects will be highlighted below.

4.1. Breatheomics

Breatheomics, the analysis of biomarkers in exhaled breath, is an emerging aspect in lung disease diagnostics. Interestingly, profiling of volatile organic compounds (VOCs) was selected by a group of severe asthma experts as one of the most important potential biomarkers for the future.[106] Examples of VOCs are ethane and pentane, which are shown to be related to oxidative stress. However, there is a wide range of exhaled biomarkers that are yet to be explored.[107] Identification of distinct VOC profiles has been shown to be successful in discriminating asthma from controls or chronic obstructive pulmonary disease (COPD), and early- from late-onset asthma.[108,109] Interestingly, exhaled breath profiling was also effective in predicting steroid responsiveness in asthma.[110] Detecting the optimal subgroup of patients for biologic response by means of VOC profiling may be a future phase in biological treatment in severe asthma.[111,112]

4.2. Genetic aspects

The last decade's insight in genomic predictors of asthma phenotypes and treatment response is growing.[113] A few pharmacogenetic studies have recently evaluated the response to asthma therapies with monoclonal antibodies.[87,114] In a GWAS using DREAM and MENSA data of mepolizumab-treated patients, a trend towards association was found between exacerbation prevention and 2 loci found on chromosomes 6 and 9, respectively UTRN, EPM2A, IFNA14 and IFNA22P. However, the biologic link to enhanced mepolizumab response is not clear for these loci.[87] Though so far only suggestive associations with MAB response are reported, the possibility of genetic screening before therapy initiation may be a next step towards personalized medicine.

4.3. Therapeutic drug monitoring (TDM)

Mechanisms underlying response or non-response not only include disease characteristics, but also drug- (immunogenicity, pharmacodynamics, and pharmacokinetics) and treatment strategy (dosing regimen) related factors.[115,116] There is a wide inter-individual variability in MAB exposure due to target burden and other factors affecting their pharmacokinetics, including the development of anti-drug antibodies (ADA).[117] TDM of MABs can be used, measuring total (free, soluble target bound and ADA bound) MAB concentration, to optimize clinical outcomes in patients in various clinical situations. [117,118] Evidence regarding the utility of TDM for MABs in the treatment of inflammatory diseases is growing steadily. In the treatment of inflammatory bowel disease and ulcerative colitis, emerging data indicate a strong relationship between drug exposure and efficacy of anti-Tumor Necrosis Factor-α (TNF-α) agents.[119–121] Different expert groups in this field suggest a role for TDM of anti-TNF-α agents in guiding treatment changes [122,123], in particular upon treatment failure following successful induction, and in clinical remission. Also in Rheumatoid Arthritis, TDM for adalimumab and infliximab plasma levels has been widely established over the past few years[124–126], based on the relationship between low MAB serum levels and non-response or ADA development.[125,127] In asthma, research into the role of TDM in optimizing MAB use is still in its infancy[128] and its utility

in early detection of non-response needs to be assessed. Yet, in line with developments in other inflammatory disease, therapeutic drug monitoring may be considered a promising tool to increase the efficacy, patient safety and cost-effectiveness of MABs in severe asthma treatment.

4.4. Data science approaches

Another option to enable evaluation of response to biological treatment in patients with severe asthma lies in the utilization of large population databases. Standardized international severe asthma registries, such as SHARP [129] and ISAR [130], may help to identify the right endotypes and biomarkers, predictive of response to specific drugs.[131]

5. Conclusion

This article summarizes the current state of knowledge on response prediction of biological treatment in severe asthma. Studies that explore the predictability of biologic efficacy are mainly based on post-hoc analyses of the large registration trials or small exploratory studies with a limited number of patients. Although these studies provide some insight, there are still several issues that require further evidence. For example, what is the best timing to assess biologic response or when can a patient be classified as non-responder? Should we keep on focusing on general response criteria or might an individualized approach be preferable, considering treatment responses on a case-by-case basis?[106] Further research should incorporate real-world data and investigate whether detailed algorithms, using baseline as well as early evaluation parameters, might improve the monitoring of treatment response and the prediction of long-term benefits. New tools have potential to contribute to response prediction, and may prove their value in the near future. Decisions on initiation and continuation of biological therapy in severe asthma are still challenging, indicating the need to better recognize the clinical relevance of phenotypes and biomarkers, both those currently available as well as those to be expected.

CRediT authorship contribution statement

J.A. Kroes: Investigation, Formal analysis, Writing - original draft, Writing - review & editing. **S.W. Zielhuis:** Conceptualization, Writing - review & editing, Supervision, Funding acquisition. **E.N. van Roon:** Writing - review & editing, Supervision. **A. ten Brinke:** Conceptualization, Writing - review & editing, Supervision.

Declaration of Competing Interest

JA Kroes: No conflicts of interest to disclose.

A ten Brinke: Unrestricted research grants GSK, TEVA. Research advisory boards GSK, Novartis, AstraZeneca, Boehringer Ingelheim, Chiesi, Sanofi. Honoraria lectures GSK, Novartis, Teva, Boehringer Ingelheim.

SW Zielhuis: Advisory boards Novartis, AstraZeneca, Sanofi. Honoraria lectures MSD. Until 2007 employed at Teva NL, but no involvement since then.

EN van Roon: No conflicts of interest to disclose.

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