

University of Groningen

Biologics in severe asthma

Rogers, Linda; Jesenak, Milos; Bjermer, Leif; Hanania, Nicola A.; Seys, Sven F.; Diamant, Zuzana

Published in:
Respiratory Medicine

DOI:
[10.1016/j.rmed.2023.107414](https://doi.org/10.1016/j.rmed.2023.107414)

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2023

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Rogers, L., Jesenak, M., Bjermer, L., Hanania, N. A., Seys, S. F., & Diamant, Z. (2023). Biologics in severe asthma: A pragmatic approach for choosing the right treatment for the right patient. *Respiratory Medicine*, 218, Article 107414. <https://doi.org/10.1016/j.rmed.2023.107414>

Copyright

Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license. More information can be found on the University of Groningen website: <https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment>.

Take-down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): <http://www.rug.nl/research/portal>. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.



Original Research

Biologics in severe asthma: A pragmatic approach for choosing the right treatment for the right patient

Linda Rogers^{a,*}, Milos Jesenak^b, Leif Bjermer^c, Nicola A. Hanania^d, Sven F. Seys^e,
Zuzana Diamant^{f,g,h,i}

^a Mount Sinai National Jewish Health Respiratory Institute, Icahn School of Medicine at Mount Sinai, New York, New York, USA

^b Department of Pediatrics, Department of Pulmonology and Phthisiology, Department of Allergology and Clinical Immunology, Jessenius Faculty of Medicine, Comenius University in Bratislava, University Teaching Hospital in Martin, Martin, Slovakia

^c Department of Respiratory Medicine and Allergology, Lund University, Lund, Sweden

^d Section of Pulmonary /Critical Care/Sleep Medicine, Baylor College of Medicine, Houston, TX, USA

^e Galenus Health, Hasselt, Belgium

^f Department Clin Pharm & Pharmacol, Univ Groningen, Univ Med Ctr Groningen, Groningen, Netherlands

^g Department of Microbiology Immunology & Transplantation, KU Leuven, Catholic University of Leuven, Belgium

^h Department of Respiratory Medicine, First Faculty of Medicine, Charles University and Thomayer Hospital, Prague, Czech Republic

ⁱ Department of Respiratory Medicine & Allergology, Institute for Clinical Science, Skane University Hospital, Lund University, Lund, Sweden



ARTICLE INFO

Keywords:

Asthma
Comorbidities
Biologics
Type 2 inflammation
Biomarkers
Asthma management

ABSTRACT

The development of monoclonal antibody therapies targeting specific components of the pathways relevant to asthma pathophysiology has revolutionized treatment of severe asthma both in adults and children and helped to further unravel the heterogeneity of this disease. However, the availability of multiple agents, often with overlapping eligibility criteria, creates a need for pragmatic guidance for specialists undertaking care of patients with severe asthma. In this review, we provide an overview of the data supporting the clinical efficacy of biologics in distinct asthma phenotypes/endotypes. We also focus on the role of biomarkers and treatable traits, including comorbidities, in the choice of asthma biologics, highlight which treatments have been demonstrated to be steroid sparing in corticosteroid dependent asthma, and provide practical guidance that can drive shared decision making on treatment choice with patients. In addition, we summarize what is known to date regarding long-term safety of these drugs, and lastly, discuss future directions in biologics research.

1. Introduction

Recent decades have seen striking advances in asthma care with the availability of effective inhaled formulations, usually consisting of inhaled corticosteroids with or without long-acting bronchodilators, which - when used correctly and consistently - prove highly effective at achieving asthma control in many patients. Although precise estimates of the percentage of patients uncontrolled on moderate to high doses inhaled corticosteroids and additional controllers are a matter of debate, it is estimated that 3–4% of patients may not achieve adequate asthma control with inhaled regimens when accounting for adherence and adequate inhaler technique [1]. In those with severe asthma, there remains a significant burden of exacerbations despite specialist care and high intensity inhaled and/or chronic oral corticosteroid therapy, with as many as 53.5% and 12.3% of such patients experiencing an

exacerbation and asthma hospitalization annually, respectively (0.81 and 0.14 per person-year) [2]. Chronic use of oral corticosteroids has been associated with adverse effects including diabetes, cardiovascular disease, infections, ocular abnormalities, osteoporosis, and psychiatric disorders [3,4]. In addition, adverse effects also occur following repeated short courses of systemic corticosteroids [5]. These sequelae associate with significant morbidity, poor quality of life, and increased consumption of health care resources [6].

Current advances in our understanding of the molecular mechanisms underlying airway inflammation have led to the development of monoclonal antibody therapies targeting these pathways, commonly referred to as biologics. Asthma is best categorized as a syndrome rather than a single disease, and attempts to subtype heterogeneity using clinical characteristics, or phenotypes, has been less effective at targeting therapies than using subtypes based on inflammatory mechanisms, or endotypes. A paradigm of 2 endotypes, type 2 high and type 2 low,

* Corresponding author.

E-mail address: linda.rogers@mssm.edu (L. Rogers).

<https://doi.org/10.1016/j.rmed.2023.107414>

Received 10 May 2023; Received in revised form 20 August 2023; Accepted 15 September 2023

Available online 29 September 2023

0954-6111/© 2023 The Authors. Published by Elsevier Ltd. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>).

Abbreviations

AERD	aspirin exacerbated respiratory disease
BEC	blood eosinophil count
CRSwNP	chronic rhinosinusitis with nasal polyposis
EGPA	eosinophilic granulomatosis and polyangiitis
FeNO	exhaled nitric oxide
HES	hyper eosinophilic syndrome
IgE	immunoglobulin E
IL-5	interleukin 5
IL-4ra	Interleukin 4 receptor alpha subunit
IL-13	Interleukin 13
OCS	oral corticosteroids
SC	subcutaneous
T2	type 2
TARC	thymus and activation-regulated chemokine
TSLP	thymic stromal lymphopoietin
VCAM	vascular cell adhesion molecule

has emerged in recent years [7]. Type 2 (T2) immune responses, attributed to subsets of CD4⁺ T cells known as T helper 2 cells (Th2) that produce interleukins 4, 5 and 13, (IL4, IL5, IL13) have classically been associated with eosinophilic airway inflammation and atopic disease [8]. More recently, T2 inflammation has been linked to innate immune responses from group 2 innate lymphoid cells (ILC2s) including in the absence of allergen sensitization.^{8f} A true prevalence of T2 inflammation in severe asthma is difficult to ascertain due to impact of therapies including inhaled and oral steroids on measures of inflammation, however estimates range from 50 to 95% of those with severe asthma [9, 10]. Biologics which target T2 inflammatory pathways are highly effective in achieving asthma control and reducing risk of exacerbations in those patients with T2 inflammation whose asthma is uncontrolled with moderate to high doses of inhaled corticosteroids and additional controller therapies [11]. These therapies target key points of the T2 inflammatory pathway including immunoglobulin E (IgE) (omalizumab), interleukin 5 (IL-5) (mepolizumab, reslizumab) or its receptor (benralizumab), thymic stromal lymphopoietin (TSLP)(tezepelumab),

and interleukin 4 receptor alpha subunit (IL4ra) (dupilumab), a common receptor for both IL-4 and interleukin 13 (IL-13) signaling.(Fig. 1). Except for tezepelumab, these therapies demonstrate efficacy only in those identified as having underlying T2 inflammation characterized by allergen-driven disease, increased blood or sputum eosinophils and/or elevated levels of fractional exhaled nitric oxide (FeNO). Tezepelumab (anti-TSLP) has clinical efficacy irrespective of the presence of T2 inflammatory biomarkers [12]. Dupilumab is also indicated for those dependent on systemic corticosteroids in whom T2 biomarkers may be suppressed [13]. Given the overlapping activities of these therapies, it falls upon specialists caring for severe asthma patients to recommend these therapies in the absence of data from direct comparative effectiveness clinical trials. In this review, we aim to provide a pragmatic framework that can be used by practicing clinicians to select therapy for an individual patient. To this end, we will provide a brief overview of the available agents approved for treatment of both adults and children, patient characteristics, predictive biomarkers, outcomes impacted by each agent, and the results of indirect comparison studies. Additionally, we will discuss safety profiles and the role of patient preferences and other factors important to shared decision making in treatment decisions. Lastly, we will review unmet needs and areas for future research.

1.1. Overview of data supporting the efficacy and effectiveness of available biologics

Over the past two decades, expansive progress in our understanding of the underlying mechanisms of asthma brought new insights into the heterogeneous nature of the disease both within individual patients over time as well as across patients. These insights helped define distinct inflammatory phenotypes and endotypes and drove the development of targeted treatment options which helped uncover new pathways and provided further insights into the complexity of asthma. When considering the addition of a biologic for an individual patient, it is helpful to recognize the target population included in phase 3 clinical trials, understand outcomes impacted by treatment, and recognize conditions occurring alongside asthma that may also be impacted by therapy. Goals of asthma therapy include control of symptoms, reduction or elimination of exacerbations, reduction of cumulative adverse effects of oral corticosteroids, and optimization of lung function. Phase 3 studies

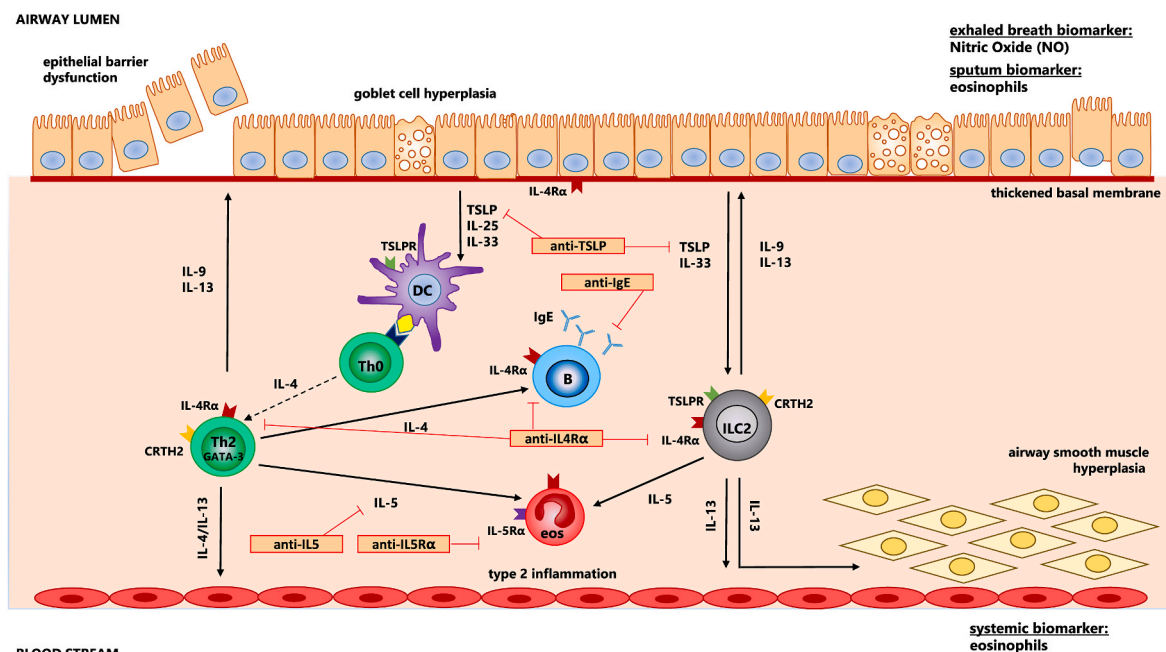


Fig. 1. Asthma biologics target key points in the type 2 inflammatory pathway.

leading to regulatory approval of asthma biologics typically enroll those with 1–2 exacerbations requiring treatment with systemic corticosteroids per year, and inadequate symptom control despite moderate to high dose inhaled corticosteroids and a second controller. An overview of data from currently approved biologics is highlighted in Table 1. The primary outcome of most studies determining regulatory approval is the rate of asthma exacerbations.

Omalizumab was approved for treatment of moderate-to-severe allergic asthma with perennial allergen sensitization. Although total IgE levels are key to dose calculation, they are not related to clinical response. While data from clinical trials suggests that levels of other T2 biomarkers, including FeNO and absolute blood eosinophil counts (BEC) > 250/ μ L, are more strongly associated with clinical response in terms of exacerbation reduction, real world studies failed to show this association [14,15]. Mepolizumab, Reslizumab and Benralizumab are effective in eosinophilic asthma (i.e. with elevated BEC), while Dupilumab is more effective in patients with T2 asthma characterized by elevated levels of eosinophils or FeNO, usually >25 ppb [16–20]. Clinical efficacy in terms of exacerbation reduction increases for all biologics with increasing levels of BEC. Tezepelumab has shown clinical efficacy in both T2 and non-T2 or T2 low asthma: i.e. with BEC <150/ μ L and FeNO levels <25 [12]. Impact of asthma biologics on other outcomes such as symptom scores and lung function parameters vary according to agent and is more modest compared to the impact on exacerbations as shown in Table 1. Considering substantial overlap of eligibility and clinical outcomes, direct comparative effectiveness studies ideally would help providers to choose amongst asthma biologics, however no

such studies have been performed. However, several indirect comparison studies have been conducted using various methodologies. Some studies have included multiple drug classes, whereas others have compared only anti-IL5 pathway therapies, and one compared Mepolizumab and Omalizumab [21–25]. Differing approaches were used to attempt to match inclusion criteria and biomarker levels, and criteria used by some studies have been criticized. Comparisons of other agents to Reslizumab are challenging due to unique inclusion criteria (BEC \geq 450/ μ L) in its phase 3 clinical trials [17]. A series of systematic reviews published by the European Academy of Allergy and Clinical Immunology (EAACI) concluded that all biologics reduce exacerbation rates with high certainty of evidence and improve asthma control, quality of life, and FEV₁ with moderate certainty [26,27]. Bayesian network analysis comparing Mepolizumab, Benralizumab, and Dupilumab in those with BEC \geq 300 and evaluating exacerbation reduction, pre-bronchodilator FEV₁, symptoms scores, and serious adverse events found most outcomes were comparable among these 3 agents [28]. In summary, based on indirect comparison studies and clinical experience of the authors, existing asthma biologics possess overlapping clinical efficacy.

1.2. Data supporting currently available biologics in children with asthma

Severe asthma in childhood, although an uncommon condition, represents a challenge. Whereas the estimates of the prevalence of severe asthma in adults is better known, its frequency in childhood is unknown. According to one definition, its prevalence in children may be

Table 1
Currently approved biologics for adults with severe asthma.

Biologic	Omalizumab	Dupilumab	Mepolizumab	Reslizumab	Benralizumab	Tezepelumab
Target	Free IgE	IL4-Ra (IL-4/IL-13)	IL-5	IL-5	IL-5 receptor	TSLP
Administration route/site	SC Home use after observed injections	SC Home use	SC Home use	Intravenous (weight based)	SC Home use	SC Home use
# Injections/Dosing interval	1-3 injections every 2–4 weeks	1 injection every 2 weeks after loading dose	1 injection monthly	1 injection monthly	1 injection monthly for 3 months and then every 8 weeks	1 injection monthly
Target population	Allergen-driven	T2 \pm CRSwNP OCS-dependent	Eosinophilic +/- CRSwNP or AERD	Eosinophilic	Eosinophilic	Uncontrolled severe asthma irrespective of biomarker status
Children indication	Age \geq 6	Age \geq 6	Age \geq 6	Age \geq 18	Age \geq 12	Age \geq 12
Predictive biomarkers	+ positive perennial allergen test	FeNO BEC	FeNO BEC Sputum eosinophils	BEC	BEC Sputum eosinophils	FeNO BEC
Reduction in ACQ (MCID 0.5) in phase 3	0.36	0.31–0.34	0.44	0.2–0.27	0.1–.29	.33
% Exacerbation reduction in phase 3 trials	25% Reduced seasonal viral exacerbations in children	46–47%	53%	50–59%	28–51%	41–56%
Improvement in pre-bd FEV ₁ (ml) in phase 3 studies	NA	130–140	98	90–126	116–159	130
Reduced BHR	Reduced BHR to mannitol
Comorbidities with treatment indication	CRSwNP	CRSwNP AD	CRSwNP	–	–	–
OCS sparing in OCS dependent asthma (vs. placebo)	NA	70.1 vs. 40.9	50 vs. 0	NA	75 vs. 25	Possible effect in those with T2-asthma
Other conditions with treatment indication	Chronic urticaria	EOE Chronic urticaria Prurigo nodularis	EGPA HES	–	–	–
References	Normansell et al. [135]	LIBERTY QUEST LIBERTY VENTURE [13,20]	MENSA SIRIUS [16,72]	Castro et al. [17]	SIROCCO CALIMA ZONDA [18,19,73]	NAVIGATOR SOURCE [12,75]

ACQ: Asthma Control Questionnaire; AERD: aspirin exacerbated respiratory disease; BEC: blood eosinophil count; BHR: bronchial hyper reactivity; CRSwNP chronic rhinosinusitis with nasal polyposis; EoE: eosinophilic esophagitis; EGPA: Eosinophilic granulomatosis with polyangiitis; FeNO: exhaled nitric oxide; FEV₁: forced exhaled volume in 1 s IgE: immunoglobulin E; HES: hyper-eosinophilic syndrome MCID: minimal clinically important difference; OCS: oral corticosteroid dependence; SC: subcutaneous; TSLP: thymic stromal lymphopoietin.

up to 5% [29]. Similar to adults, affected children experience a significant disease burden, morbidity, and negative impact on quality of life [30]. When evaluating all of those with uncontrolled asthma, but especially children, several questions come up: 1) Is this really asthma? 2) Are there any comorbidities/treatable traits that should be addressed? 3) Is there optimal compliance and inhalation technique? 4) Is there a chronic exposure to environmental triggers? 5) Is the asthma steroid-responsive? [31] Several challenges are presented in the evaluation and management of children with severe asthma, e.g., incorrect diagnosis (not every wheeze is asthma), disease acceptance (by parents and/or by the child), different inhalation techniques and devices (compared to adults), concerns regarding possible adverse effects of therapy (growth retardation for corticosteroids, potential neurological effects of leukotriene receptor modifiers), and the absence of reliable biomarkers and limitations of lung function testing in younger age categories [32,33]. After excluding conditions that mimic severe asthma (e.g., recurrent viral infections with wheezing, congenital airway malformations and vascular rings, cystic fibrosis, primary ciliary dyskinesia, gastroesophageal reflux, foreign body aspiration or primary immunodeficiencies), one must face a big challenge – personalised treatment approaches including biologics. In general, especially in younger age groups, evidence supporting use of selected therapies (classic controllers and biologics) is limited and many of the therapies have strict age limitations for their use from a regulatory standpoint. One should aim to treat a child with severe asthma, not only effectively, but also safely. Currently available biologics for children have different age indications, dosage schedules and inter-dose intervals, while data from clinical trials show variable clinical effects (Table 2) [34–36]. One of the most important questions in the management of severe asthma in children is whether these biologics are expected to be administered for lifetime or only for a limited period. It has been postulated that more intensive treatment in earlier asthma could lead to induction of long-lasting remission, but this has not been confirmed. Some studies and reports suggest that biologics might be discontinued in a selected group, however, selection criteria or biomarkers identifying appropriate candidates remain unclear [37–39].

1.3. Selecting the right biologic

When selecting a biologic for a particular patient, it is necessary to integrate results of biomarker assessments, comorbid conditions, presence of oral steroid dependence, and various patient factors as illustrated in Fig. 2. Below we discuss each of these aspects and how they impact choice of therapy.

1.4. Biomarkers

The initial failure of anti-IL5 biologics in clinical trials, followed by the success of clinical trials where patients were included based on confirmation of eosinophilia highlights the importance of biomarkers in selecting patients for asthma biologics [40]. Omalizumab was the first agent to use a biomarker for treatment eligibility, requiring a specific range of total IgE level and the presence of perennial allergen sensitization confirmed by allergen-specific IgE or skin prick testing (Table 1). Although the level of total IgE and the number of sensitizations to perennial allergens can to some extent predict more severe asthma, neither total IgE levels nor allergen sensitization numbers predict response to therapy [41]. Post-hoc analysis of clinical trials, demonstrated that T2 biomarkers, including fraction of exhaled nitric oxide (FeNO) ≥ 19.5 parts per billion (ppb) and blood BEC $\geq 260/\mu\text{L}$, were associated with improved efficacy of omalizumab as determined by exacerbation reduction [14]. However, as mentioned above, in real world studies, clinical response to Omalizumab was independent of elevation of T2 biomarkers [15]. However, high blood and sputum eosinophils predict increase risk of asthma exacerbations, airway remodeling and lung function decline in addition to predicting response to most available biological [42–45]. FeNO is another T2 biomarker with prognostic, predictive, and pharmacodynamic properties. It is produced by bronchial epithelial cells via activation of the STAT-6 pathway by type 2 cytokines including IL-4 and IL-13, driving production of inducible nitric oxide synthase [46]. Thus, FeNO serves as a biomarker for IL-4/IL-13 driven airway inflammation, and its levels have been similarly associated with airway remodeling, lung function decline, and increased risk of asthma exacerbations [46–48]. While baseline FeNO levels may not predict the response to anti-IL-5 therapies higher baseline

Table 2

Currently approved biologics for children and adolescents with severe asthma and their effect on disease characteristics [16,34–36,131,136–139].

Biologic	Omalizumab	Dupilumab	Mepolizumab	Benralizumab	Tezepelumab
Target	IgE	IL4-Ra (IL-4/IL-13)	IL-5	IL-5 receptor	TSLP
Administration route/site	Subcutaneous Home use after observed injections	Subcutaneous Home use	Subcutaneous Home use	Subcutaneous Home use	Subcutaneous Home use
^a Injections/Dosing interval	Depends on blood total IgE and weight 1-3 injections every 2–4 weeks	1 injection (200 or 300 mg) every 2 weeks after loading dose	1 injection (40 or 100 mg) monthly	1 injection monthly x 3 then every 8 weeks	1 injection (210 mg) monthly
Age indication	Age ≥ 6	Age ≥ 6 (US FDA) Age ≥ 12 (EMA)	Age ≥ 6	Age ≥ 12	Age ≥ 12
Improved asthma control^b	yes	yes	yes	yes	Yes
Exacerbation reduction (%)^b	↓ (~30–60%)	↓ (~30–60%)	↓ (up to 50%)	↓ (36–63%)	↓ (up to 70%)
Improvement in pre-bd FEV₁ (ml)^b	no improvement	↑ (130–320)	↑ in ≥ 12 years (98–120) No change in 6–11 years	↑ (116–256)	↑ (130–230)
Impact on biomarkers	↓ FeNO ↓ BEC	↓↓ FeNO ↓↓ BEC ^a ↓ total IgE ↓ (~ 70%)	↓ FeNO ↓ BEC	↓↓ FeNO ↓ BEC	↓ FeNO ↓ BEC ↓ total IgE No effect
OCS use^b	↓ (~30–100%)	↓ (~ 70%)	↓ (~ 50%)	↓ (75%)	No effect
Comments	More evidence in children compared to other biologics	Increasing evidence in children (children with atopic dermatitis approved ≥ 6 years)	Greater bioavailability in children 6–11 years		Limited data for adolescents

BEC: blood eosinophil count; FeNO: exhaled nitric oxide FEV₁: forced exhaled volume in 1 s; IgE: immunoglobulin E; OCS: oral corticosteroid dependence; TSLP: thymic stromal lymphopoeitin.

^a transient increase of blood eosinophilia in proportion of the patients, which normalized in the majority of treated subjects.

^b data from mixed adult and adolescent populations with domination of adults in these outcomes.

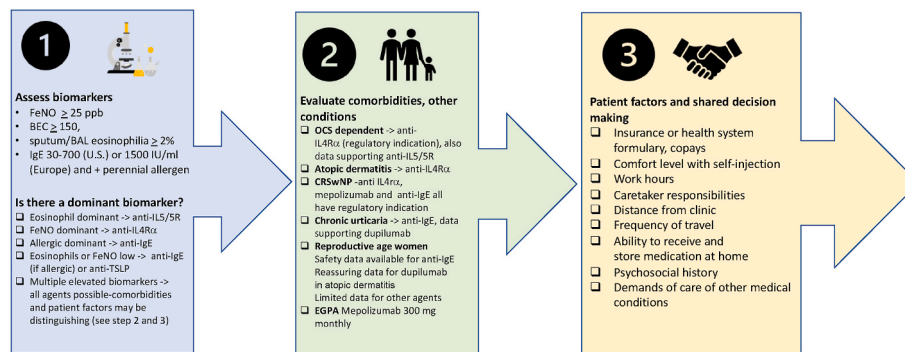


Fig. 2. A pragmatic approach to choosing an asthma Biologic.

levels of FeNO (>25 ppb) predict the clinical response to Dupilumab [49–51]. Increased levels of multiple T2 biomarkers, including BEC, FeNO, IL-5, IL-13 and periostin have all been predictive of response to Tezepelumab [52].

Uniquely, Tezepelumab reduced asthma exacerbations despite low levels of T2 biomarkers including FeNO <25 ppb and BEC $<150/\mu\text{L}$ unlike most other asthma biologics [12]. Based on these findings and expert experience, some have suggested that presence of a dominant biomarker, defined by marked elevation of FeNO or BEC in the presence of modest or no elevation of the other biomarker should direct treatment to Dupilumab if the dominant biomarker is FeNO or anti-IL-5 if it is BEC [53–55]. Modest elevations of FeNO and blood eosinophils predict response to all available agents whereas Tezepelumab and Omalizumab may be used with FeNO <25 ppb and BEC $<150/\mu\text{L}$ in the presence of sensitization to a perennial aeroallergen for the latter.

Biomarkers also have important pharmacodynamic effects. Whereas blockade of anti-IL5 or its receptor results in decrease in eosinophil counts with absent or modest effects on FeNO, Dupilumab reduces FeNO and IgE levels while blood eosinophils remain unchanged or transiently increase [47–49]. Blockade of IL-4 and IL-13 with Dupilumab inhibits eosinophil tracking to tissues via blockade of vascular cell adhesion molecule (VCAM)-1, eotaxin-3, thymus and activation-regulated chemokine (TARC) without impact on bone marrow production of eosinophils and may account for these observations [56]. Tezepelumab reduces blood eosinophils, FeNO and IgE levels [52]. In summary, biomarkers have prognostic, predictive and pharmacodynamic properties that can be used to facilitate the choice of biologics in severe asthma [57, 58].

1.5. Comorbidities

The more severe – usually late onset – asthma subtypes often present with more comorbid conditions which may be causal or coexistent. The presence of these comorbidities, some of which have separate indications for various biologics, may help direct selection of therapy when more than one condition is present [59]. Chronic rhinosinusitis with nasal polyposis (CRSwNP) coexists in over 30% of persons with severe asthma, with or without aspirin exacerbated respiratory disease (AERD) [60]. CRSwNP has a high rate of recurrence after sinonasal surgery, can be refractory to topical nasal therapies, and can be effectively treated by biologics, with Dupilumab, Omalizumab and Mepolizumab having a regulatory indication separate from asthma [61–63]. The presence of CRSwNP is also a predictor of response of asthma to treatment with anti-IL-5 and Dupilumab [64,65]. Apart from CRSwNP, Dupilumab has several additional non-asthma treatment indications including atopic dermatitis, eosinophilic esophagitis, prurigo nodularis [66–68]. Apart from indications for allergic asthma and CRSwNP, Omalizumab is also indicated for chronic urticaria [69]. Mepolizumab has additional indications for hypereosinophilic syndrome (HES) and eosinophilic granulomatosis and polyangiitis (EGPA) [69,70]. Although

HES is not specifically associated with asthma, asthma and nasal polyposis are clinical criteria that are part of diagnosis of EGPA and may be the earliest manifestations in the eosinophilic phase of the disease prior to identification of vasculitis [71]. EGPA should be considered in patients with eosinophilic asthma and nasal polyposis with migratory pulmonary infiltrates, high BEC (>1000 – 1500 cells/ μL) and potentially related clinical findings outside of the respiratory tract (neuropathy, thromboembolic disease, cardiac, renal, or gastrointestinal involvement). A detailed review of systems to identify potentially related comorbid conditions is critical to the evaluation of severe asthma patients being considered for biologic therapies as shown in Fig. 2. Identification of other health conditions including sinonasal disease, skin conditions, and other eosinophilic disorders may impact choice of biologics as the patient may have more than one condition that may benefit from specific treatments.

1.6. OCS-dependent asthma

Three phase 3 clinical trials have demonstrated systemic corticosteroid sparing efficacy of asthma biologics, specifically Mepolizumab, Benralizumab, and Dupilumab. In the SIRIUS study, median percentage reduction from baseline in the maintenance systemic corticosteroid (OCS) dose was 50% in the mepolizumab group versus no reduction in the placebo group [72]. The ZONDA study found a 75% reduction in OCS dose versus 25% with placebo [73]. VENTURE found a 70% reduction in the OCS maintenance dose in dupilumab treated participants compared with a 42% decrease in those treated with placebo [13]. Dupilumab is currently the only asthma biologic that has a specific regulatory indication for OCS dependent asthma without a biomarker requirement which creates certain practical advantages as blood eosinophilia can be masked in those who use chronic maintenance OCS [74]. Based on these data, Mepolizumab, Benralizumab, or Dupilumab should be preferred choices to treat OCS dependent asthma. SOURCE, the phase 3 study evaluating corticosteroid sparing efficacy of Tezepelumab, did not meet its primary endpoint of exacerbation reduction [75]. However, analysis stratified by T2 biomarkers suggested possible corticosteroid sparing effect in those with increased BEC and/or FeNO.

1.7. Patient factors in selection of biologics

After considering biomarkers and comorbid conditions, patients may continue to be eligible for multiple classes of asthma biologics. As part of shared decision making, patient characteristics, preferences, and other life factors should be factored into choice of treatment (Fig. 2). Two key factors are the frequency of injection and location of administration. Mepolizumab, Benralizumab, Dupilumab, and Tezepelumab are all approved for home administration but can be administered optionally in medical settings depending on patient needs [74,76–78]. Reslizumab, an intravenous therapy, is approved for administration in a medical setting [79]. Although for many years Omalizumab was primarily

administered in a medical setting, home use has now been approved under certain conditions [80]. It is recommended that patients not have a prior history of anaphylaxis and that they undergo at least three injections in a medically supervised setting prior to home administration. Tezepelumab, initially approved for administration in a medical center, is now approved for home use [78]. Mepolizumab is administered monthly, Benralizumab monthly for 3 months and then every 8 weeks, Dupilumab is dosed every 2 weeks, and Tezepelumab is administered monthly. Dosing frequency of Omalizumab for asthma depends on a nomogram including total IgE level and weight. Patients may need as little as one injection monthly or as many as 3 injections every 2 weeks. Patient factors such as work hours, caretaker demands, frequency and duration of work or personal travel, and ability to receive delivery and properly store medication are all factors that can be considered when choosing therapy for a particular patient. For example, for patients who are fearful of injections, those with multiple comorbidities and complex medical regimens, or those who have complex travel schedules, administration of Benralizumab every 8 weeks after an initial 3-month induction phase may be more convenient. Patients who have visual, manual, cognitive or emotional barriers to self-injection and do not have a caretaker to assist may be better suited to receive therapy in a medical setting. Patients with living circumstances that impede reliable delivery or storage of medications or those who have psychological or social barriers to treatment may benefit from dosing in a clinical setting as frequent health system contact may support adherence and provide additional benefits in terms of monitoring and provision of social services in tandem with treatment. This is especially important as studies suggest socioeconomic disparities in prescribing of asthma biologics to those with higher income and access to specialists despite the high frequency of poorly controlled asthma in socially disadvantaged groups [81]. Regular visits to monitor asthma stability and taper OCS in patients with OCS dependent asthma may favor clinic administration for certain patients. Those patients who live far from specialty centers, who travel frequently, or have work or care responsibilities that may limit their ability to attend clinic visits may favor home use. A shared decision-making tool is available for use to help guide these decisions [82]. Lastly, but quite important in light of cost of these treatments, are health insurance coverage, payer formularies and patient copayments, all of which may dictate initial treatment selection.

An additional patient characteristic that may influence biologic choice is likelihood of pregnancy during treatment. Those with asthma of sufficient severity to consider a biologic are also a group of patients in whom uncontrolled asthma may increase adverse pregnancy outcomes [83]. In these cases, providers must balance the known benefits of asthma control in pregnancy, potential adverse effects of OCS, and lack of safety data for most asthma biologics during pregnancy. Reassuring data has been published from the EXPECT registry on safety of Omalizumab in pregnancy and use of Dupilumab during pregnancy in patients with atopic dermatitis is also reassuring [84,85]. Immunology of pregnancy is complex; however it is known that local and systemic balance between effector type 1/type2/type 3 T cells and regulatory T cell subsets are essential for a healthy pregnancy [86]. Although animal studies of current biologics have not raised major concerns, given the potential impact of these treatments on these pathways, there is cause for at least theoretical concern that these could impact the course of a pregnancy. Current asthma biologics include monoclonal antibodies of the IgG1 (Omalizumab, Mepolizumab, and Benralizumab), IgG4 (Reslizumab and Dupilumab), and IgG2λ (Tezepelumab) subclasses. Placental transport of IgG is dependent on the Fc portion and efficacy is as follows: IgG1>IgG4>IgG3>IgG2 [86]. Although the degree of placental transport may differ, exposure of the developing fetus to drug is likely. Moreover, clearance of monoclonal antibody therapeutics occurs predominantly via the reticuloendothelial system which is underdeveloped in the fetus, making it likely that any biologic that crosses the placenta may be cleared slowly and may accumulate to greater levels in the fetus [86]. These concerns should be balanced with robust data

suggesting that maternal asthma control is crucial to pregnancy outcomes in women with severe asthma [83]. Importantly, at least one study suggests that level of control of maternal asthma may impact risk of wheezing illness and asthma in children of mothers with asthma [87]. Decisions may depend on underlying severity of asthma and course of asthma during prior pregnancies. Optimally the ideal time to discuss these complex decisions are prior to initiating a biologic and prior to pregnancy. A clear understanding regarding whether the patient would opt to remain on therapy or discontinue during pregnancy should be discussed. If discontinuation prior to conception to avoid fetal exposure is preferred by the patient, education regarding the long half-life of these drugs, careful family planning, and discontinuation several months prior to conception is needed.

1.8. Assessing response to biologics

Among the most vexing issues around treatment with biologics is in regard to questions on how and when to best assess response to treatment, and when and how to switch therapies in cases of treatment failure. There is currently no universally accepted definition of response, a dearth of direct studies specifically addressing these questions, and guidance suggested for providers is largely extrapolated from inclusion criteria and response to various outcomes in clinical trials, data from observational cohort studies, and expert opinion [88,89]. A recent systematic review by 3 TR Asthma Definition of Response Working Group highlights this area as an unmet research need and reviews a number of composite outcome measures (ASSESS, CASI, FEOS), as no single measure, whether exacerbations, lung function, or symptom scores adequately captures the multiple facets of response to therapy [90]. Of note, most composite measures lack an assessment of quality of life and none were developed with patient input [90].

This question is further complicated by a number of issues. First, there is significant placebo effect observed in most randomized clinical trials for biologics highlights that factors apart from drug efficacy are influencing outcomes in clinical trials. Second, real-world treatment has expanded beyond patient populations studied in clinical trials. For example, exacerbations rates, the primary end point for most biologics clinical trials, are not required by some payors or countries, and broader use of these agents, such as in those with refractory symptoms and/or persistent severe lung function deficits without exacerbations, occurs where permitted. For those patients on chronic OCS, a reduction in OCS dose is an important consideration, and a reduction in exacerbation rates are considered primary criteria, the latter which may require at least 6–12 months to assess accurately. Response to validated symptom questionnaires, such as the Asthma Control Questionnaires (ACQ) and the Asthma Control Test (ACT) are factors most agree should be measured, however group changes in the minimal clinically important difference of these measures in biologic clinical trials that show benefit in terms of exacerbations is variable and validation of a minimal clinically important difference (MCID) for these measures in biologics-treated patients has not been performed. There is an apparent discordance between lung function response and benefit in terms of exacerbations, specifically for Dupilumab [91]. Anti-IL-5 therapies universally reduce blood eosinophil counts irrespective of clinical response to therapy, and thus are not useful to measure response to therapy. Evaluation of other biomarkers as indicators of therapeutic response is ongoing. The Global Initiative for Asthma (GINA) Difficult-to-Treat and Severe Asthma Guideline 2022 makes a pragmatic recommendation of an initial therapeutic trial for at least 4 months, with an extended trial of 6–12 months if response is unclear at 4 months, using impact on exacerbations, rates, OCS dose if on chronic OCS, and validated symptom measures (ACQ or ACT) [92]. A recent Delphi consensus report suggests to use clinical evaluation, lung function measurement, biomarker assessment, and sputum eosinophil and neutrophil counts when possible [93]. The authors agree with these pragmatic recommendations pending further data. We would also include assessment of response of

non-asthma comorbidities (atopic dermatitis, urticaria, nasal polyposis, and eosinophilic esophagitis) to promote a holistic approach to care.

1.9. Switching and combining biologics

Once a determination of partial or no-response has been made after an assessment of 4–12 months, the next question becomes whether to switch or add therapy. Moreover, some patients may experience loss of control and exacerbations after an initial apparent response to therapy. Most data on outcomes of switching among asthma biologics come from open label prospective studies, observational studies, or case series, with most data supporting clinical benefit from switches from Omalizumab to anti-IL5 therapies after an incomplete or failed response to Omalizumab [94–96]. In light of long half-life of most biologics, if direct switching without a washout occurs, as is common in clinical settings, one may inadvertently be assessing dual therapy immediately after a switch, with a 6–12 month assessment to accurately assess response to new therapy needed. Less data is available on switches from Omalizumab or anti-IL5 therapies to Dupilumab or Tezepelumab due to the more recent approvals of these treatments. Of note, there have been no clinical trials of safety and efficacy of combination therapy, with most experience reported via observational studies and case series with some reported successes [97]. Limited preliminary data suggest this may be safe, unlike the experience with rheumatoid arthritis and inflammatory bowel disease, where increased risks of infectious complications have been observed with combination biologic therapy [98]. Clinical trials combining Dupilumab and Itepekimab, an anti-interleukin 33 (IL-33) monoclonal antibody, did not report and increased adverse events [99]. Of note, combining therapies is not permitted in some countries or by certain payors [100]. Some experts recommend a reassessment at time of treatment failure or incomplete response, or deterioration of response which may include airway inflammatory cell counts retrieved by sputum induction or bronchoscopy, and imaging and/or bronchoscopy for assessment of other complicating disorders. Some experts have suggested assessment of airway autoimmunity, which may only be available in specialized centers, and measurement of neutralizing drug antibodies, reported in 1–4% of participants in clinical trials, although assays to perform this testing are not currently available by manufactures of biologics [101].

1.10. Long term efficacy, effectiveness and safety data

To date, substantial data exist regarding the safety of biologics used to treat severe asthma. In addition to data from phase 3 trials used for regulatory approval, post-phase 3 extension studies, real-world registry data, and post-marketing programs provide additional efficacy and safety data. At the time of publication of this review, twenty years of clinical experience and published systematic reviews have supported sustained efficacy and safety of Omalizumab [102,103]. Studies outlining safety after 5 or more year of continuous therapy have been published for Mepolizumab and Benralizumab [104–107]. Data on safety and efficacy after 3 years of treatment have been published for Dupilumab [56]. The most common adverse effect across drug classes are injection site reactions that rarely cause cessation of therapy. Anaphylaxis occurred in 0.1–0.3% of patients with Reslizumab and Omalizumab [79,80]. Milder hypersensitivity reactions are described for most agents at rates <1% [74,76–80]. Upper respiratory tract related symptoms, flu-like symptoms, and myalgias are reported in 3% or fewer participants across agents. Concerns about immunosuppression leading to infections or malignancy that are concerns with other classes of monoclonal antibody therapies have not been identified as significant issue with asthma biologics. Keratitis (4%), conjunctivitis (1%), and herpes viral infections were reported in patients receiving Dupilumab vs. 1% or less of those receiving placebo [74]. Increased risk of parasitic infections with anti-eosinophil/anti-T2 biologics has been a concern, and evaluation for and treatment of parasitic infections has been

encouraged prior to treatment, however, to date a significant signal of increased risk has not been reported [108]. Significant increases in blood eosinophil counts are reported in patients treated with Dupilumab, with increases $\geq 5000/\mu\text{L}$ in <1% of participants, however most increases were not associated with symptoms and returned to pretreatment levels on follow-up [109]. Although in many cases eosinophilia was asymptomatic, detected on routine lab monitoring during clinical trials, rare post marketing reports of cases of very high eosinophil counts associated with worsening asthma and sinonasal symptoms, or more serious eosinophilic pneumonia or EGPA-like presentations have been described, particularly in association with those with asthma and nasal polyposis [110,111]. These seemed to occur in OCS dependent patients switched from anti IL-5 to Dupilumab and may represent unmasking of latent EGPA. Some cases responded to dual treatment with Dupilumab and concomitant Benralizumab. Although there is no formal recommendation to monitor BEC with Dupilumab treatment, BEC $\geq 1500/\mu\text{L}$ was reported in 25% of patients and BEC >3000 in and 6.3% of patients in one study with infrequent, but significant clinical correlates in some cases [112]. It is practice of some of the authors to monitor eosinophil counts with treatment. DESTINATION, a long-term follow-up of the phase 3 Tezepelumab program which uniquely maintained an ongoing placebo arm, showed sustained reduction in exacerbations over 2 years, with lower rates of serious adverse events in those who received Tezepelumab treatment compared to placebo [113]. Across asthma biologics extension studies, rates of serious adverse effects resulting in treatment discontinuation remained low and did not increase with exposure time. As with many monoclonal antibody therapeutics, low rates of anti-drug antibodies are reported, under 5%, with lower rates of neutralizing antidrug antibodies that may be associated with more rapid rate of breakdown of drug. For most currently available biologics, there is little information regarding safety in pregnancy and during breast feeding as previously discussed, and ongoing pregnancy registries are in place for most therapies. Real-world studies looking out outcomes of biologics, including both safety and efficacy, have been reported and most support the findings of the phase 3 clinical trials [114–119]. This is important considering the highly restrictive criteria for eligibility for phase 3 studies and supports that results of explanatory trials and outcomes in terms of safety and efficacy can be generalized to typical clinical practice.

1.11. The future

The observation of ‘super responders’ to biologics, a state with one proposed definition including presence of at least 2 of 3 major criteria included exacerbation elimination, an improvement in asthma control $\geq 2x$ the minimal clinically important difference, and cessation of maintenance of oral steroids (or weaning to adrenal insufficiency), has raised our eyes to the tantalizing hope of achieving asthma remission [93,120]. Other systems proposed to assess response to biologics, including the various composite scores highlight work progressing in this space [90, 121]. More recently, several reports have tried to define and harmonize the concept of clinical remission based on real life data captured in large registries [122,123]. Harmonization across data and experts will be required on the topic of clinical and biological remission. Another fascinating yet controversial question is whether biologics may prevent development of airway remodeling/accelerated decline of lung function potentially altering the natural history of the disease [124,125]. Novel measures of treatment impact using chest CT and MRI imaging are under investigation including in clinical trials for Tezepelumab (NCT05280418), Benralizumab (NCT03976310), and Dupilumab (NCT0440318) [126–128]. These include quantitative measures of both large and small airway function and mucus plugging scores. An important consideration, particularly in young children, as to whether treatment with biologics requires lifelong continuation or whether therapy can be discontinued in some patients [129–131]. Whether this is possible at all, and how those eligible for discontinuation might be

identified is also an area of active research. The development of molecules impacting additional pathways implicated in asthma pathogenesis, including but not limited to anti-IL6, the IL-33/ST2 pathway, OX40 ligand, among others continues apace [132–134]. The addition of biologics to the therapeutic armamentarium has helped achieve asthma control in patients whose condition remained uncontrolled with prior therapies, and the hope of possibly altering the natural history of this disease creates great hope for the future of asthma care.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

CRediT authorship contribution statement

Linda Rogers: Writing – original draft, Visualization, Writing – review & editing. **Milos Jesenak:** Writing – original draft, Visualization. **Leif Bjermer:** Writing – review & editing. **Nicola A. Hanania:** Writing – review & editing. **Sven Seys:** Writing – original draft, Visualization. **Zuzana Diamant:** Writing – original draft, Writing – review & editing, review and editing.

Declaration of generative AI and AI-assisted technologies in the writing process

None.

Declaration of competing interest

Dr. Linda Rogers receives research funding including salary support from Sanofi (Global) and Gene DX (formerly Sema 4). She has served on advisory boards and performed consulting work for Astra Zeneca, Sanofi (US) and Teva Pharmaceuticals. She has received travel funding and lecture honoraria from the American College of Chest Physicians.

Dr. Sven Seys company receives grants/contracts from Sanofi, Novartis, GSK, and is an employee of Galenus Health and Hippo Dx, and received speakers fee from Teva Pharmaceuticals.

Dr. Milos Jenesak has performed consulting for Novartis, Sanofi Genzyme, Astra Zeneca, and GSK, has received payment/honoraria for lectures, presentatios, speakers bureaus, manuscript writing or educational events from Sanofi Genzyme and Novartis.

Dr. Hanania's institution receives grants or contract from Astra Zeneca, GSK, Sanofi, Genentech, and Teva and consulting fees from Astra Zeneca, GSK, Sanofi, Genentech, Teva, and Amgen, and speaking fees from Regeneron.

Dr. Bjermer has no conflicts to declare in relation to this manuscript.

Dr. Zuzana Diamant received speaker or consultant honoraria and/or served on advisory boards at: Antabio, Arcede, Foresee Pharmaceuticals, GlaxoSmithKline, Hippo-Dx, QPS-Netherlands, Sanofi-Genzyme-Regeneron, all outside the submitted work. During the last 3 years of her assignment as Research Director Respiratory and Allergy, QPS-Netherlands received European grant from ERA4TB and funding from Foresee Pharmaceuticals for early clinical studies. She serves as associate editor for Allergy and Respiratory Medicine and acts as Chair of the Asthma Expert Panel at EUFOREA. **submitted work.**

References

- [1] P.P.W. Hekking, R.R. Wener, M. Amelink, A.H. Zwinderman, M.L. Bouvy, E. H. Bel, The prevalence of severe refractory asthma, *J. Allergy Clin. Immunol.* 135 (4) (2015) 896–902, <https://doi.org/10.1016/j.jaci.2014.08.042>.
- [2] J. Trevor, N. Lugogo, W. Carr, et al., Severe asthma exacerbations in the United States: incidence, characteristics, predictors, and effects of biologic treatments, *Ann Allergy Asthma Immunol Off Publ Am Coll Allergy Asthma Immunol* 127 (5) (2021) 579–587, <https://doi.org/10.1016/j.anai.2021.07.010>, e1.
- [3] T. Volmer, T. Effenberger, C. Trautner, R. Buhl, Consequences of long-term oral corticosteroid therapy and its side-effects in severe asthma in adults: a focused review of the impact data in the literature, *Eur. Respir. J.* 52 (4) (2018), 1800703, <https://doi.org/10.1183/13993003.00703-2018>.
- [4] E.R. Bleeker, A.N. Menzies-Gow, D.B. Price, et al., Systematic literature review of systemic corticosteroid use for asthma management, *Am. J. Respir. Crit. Care Med.* 201 (3) (2020) 276–293, <https://doi.org/10.1164/rccm.201904-0903SO>.
- [5] D. Price, M. Castro, A. Bourdin, S. Fucile, P. Altman, Short-course systemic corticosteroids in asthma: striking the balance between efficacy and safety, *Eur. Respir. Rev.* 29 (155) (2020), 190151, <https://doi.org/10.1183/16000617.0151-2019>.
- [6] K. Al Efraij, K.M. Johnson, D. Wiebe, M. Sadatsafavi, J.M. FitzGerald, A systematic review of the adverse events and economic impact associated with oral corticosteroids in asthma, *J Asthma Off J Assoc Care Asthma* 56 (12) (2019) 1334–1346, <https://doi.org/10.1080/02770903.2018.1539100>.
- [7] J. Lötvall, C.A. Akdis, L.B. Bacharier, et al., Asthma endotypes: a new approach to classification of disease entities within the asthma syndrome, *J. Allergy Clin. Immunol.* 127 (2) (2011) 355–360, <https://doi.org/10.1016/j.jaci.2010.11.037>.
- [8] J.V. Fahy, Type 2 inflammation in asthma—present in most, absent in many, *Nat. Rev. Immunol.* 15 (1) (2015) 57–65, <https://doi.org/10.1038/nri3786>.
- [9] J. Corren, R.F. Lemanske, N.A. Hanania, et al., Lebrikizumab treatment in adults with asthma, *N. Engl. J. Med.* 365 (12) (2011) 1088–1098, <https://doi.org/10.1056/NEJMoa1106469>.
- [10] L.G. Heaney, J. Busby, C.E. Hanratty, et al., Composite type-2 biomarker strategy versus a symptom-risk-based algorithm to adjust corticosteroid dose in patients with severe asthma: a multicentre, single-blind, parallel group, randomised controlled trial, *Lancet Respir. Med.* 9 (1) (2021) 57–68, [https://doi.org/10.1016/S2213-2600\(20\)30397-0](https://doi.org/10.1016/S2213-2600(20)30397-0).
- [11] Global Strategy for Asthma Management and Prevention. www.ginasthma.org, 2023.
- [12] A. Menzies-Gow, J. Corren, A. Bourdin, et al., Tezepelumab in adults and adolescents with severe, uncontrolled asthma, *N. Engl. J. Med.* 384 (19) (2021) 1800–1809, <https://doi.org/10.1056/NEJMoa2034975>.
- [13] K.F. Rabe, P. Nair, G. Brusselle, et al., Efficacy and safety of dupilumab in glucocorticoid-dependent severe asthma, *N. Engl. J. Med.* 378 (26) (2018) 2475–2485, <https://doi.org/10.1056/NEJMoa1804093>.
- [14] N.A. Hanania, S. Wenzel, K. Rosén, et al., Exploring the effects of omalizumab in allergic asthma: an analysis of biomarkers in the EXTRA study, *Am. J. Respir. Crit. Care Med.* 187 (8) (2013) 804–811, <https://doi.org/10.1164/rccm.201208-1414OC>.
- [15] T.B. Casale, A.T. Luskin, W. Busse, et al., Omalizumab effectiveness by biomarker status in patients with asthma: evidence from prospero, A prospective real-world study, *J. Allergy Clin. Immunol. Pract.* 7 (1) (2019) 156–164, <https://doi.org/10.1016/j.jaip.2018.04.043>, e1.
- [16] H.G. Ortega, M.C. Liu, I.D. Pavord, et al., Mepolizumab treatment in patients with severe eosinophilic asthma, *N. Engl. J. Med.* 371 (13) (2014) 1198–1207, <https://doi.org/10.1056/NEJMoa1403290>.
- [17] M. Castro, J. Zangrilli, M.E. Wechsler, et al., Reslizumab for inadequately controlled asthma with elevated blood eosinophil counts: results from two multicentre, parallel, double-blind, randomised, placebo-controlled, phase 3 trials, *Lancet Respir. Med.* 3 (5) (2015) 355–366, [https://doi.org/10.1016/S2213-2600\(15\)00042-9](https://doi.org/10.1016/S2213-2600(15)00042-9).
- [18] E.R. Bleeker, J.M. FitzGerald, P. Chaney, et al., Efficacy and safety of benralizumab for patients with severe asthma uncontrolled with high-dose inhaled corticosteroids and long-acting β_2 -agonists (SIROCCO): a randomised, multicentre, placebo-controlled phase 3 trial, *Lancet* 388 (10056) (2016) 2115–2127, [https://doi.org/10.1016/S0140-6736\(16\)31324-1](https://doi.org/10.1016/S0140-6736(16)31324-1).
- [19] J.M. FitzGerald, E.R. Bleeker, P. Nair, et al., Benralizumab, an anti-interleukin-5 receptor α monoclonal antibody, as add-on treatment for patients with severe, uncontrolled, eosinophilic asthma (CALIMA): a randomised, double-blind, placebo-controlled phase 3 trial, *Lancet* 388 (10056) (2016) 2128–2141, [https://doi.org/10.1016/S0140-6736\(16\)31322-8](https://doi.org/10.1016/S0140-6736(16)31322-8).
- [20] M. Castro, J. Corren, I.D. Pavord, et al., Dupilumab efficacy and safety in moderate-to-severe uncontrolled asthma, *N. Engl. J. Med.* 378 (26) (2018) 2486–2496, <https://doi.org/10.1056/NEJMoa1804092>.
- [21] E.D. Bateman, A.H. Khan, Y. Xu, et al., Pairwise indirect treatment comparison of dupilumab versus other biologics in patients with uncontrolled persistent asthma, *Respir. Med.* 191 (2022), 105991, <https://doi.org/10.1016/j.rmed.2020.105991>.
- [22] I.H. Iftikhar, M. Schimmel, W. Bender, C. Swenson, D. Amrol, Comparative efficacy of anti IL-4, IL-5 and IL-13 drugs for treatment of eosinophilic asthma: a network meta-analysis, *Lung* 196 (5) (2018) 517–530, <https://doi.org/10.1007/s00408-018-0151-5>.
- [23] Y. Cabon, N. Molinari, G. Marin, et al., Comparison of anti-interleukin-5 therapies in patients with severe asthma: global and indirect meta-analyses of randomized placebo-controlled trials, *Clin Exp Allergy J Br Soc Allergy Clin Immunol* 47 (1) (2017) 129–138, <https://doi.org/10.1111/cea.12853>.
- [24] W. Busse, G. Chupp, H. Nagase, et al., Anti-IL-5 treatments in patients with severe asthma by blood eosinophil thresholds: indirect treatment comparison, *J. Allergy Clin. Immunol.* 143 (1) (2019) 190–200.e20, <https://doi.org/10.1016/j.jaci.2018.08.031>.
- [25] S.M. Cockle, G. Stynes, N.B. Gunsoy, et al., Comparative effectiveness of mepolizumab and omalizumab in severe asthma: an indirect treatment comparison, *Respir. Med.* 123 (2017) 140–148, <https://doi.org/10.1016/j.rmed.2016.12.009>.
- [26] I. Agache, J. Beltran, C. Akdis, et al., Efficacy and safety of treatment with biologics (benralizumab, dupilumab, mepolizumab, omalizumab and reslizumab) for severe eosinophilic asthma. A systematic review for the EAACI

- Guidelines - recommendations on the use of biologicals in severe asthma, *Allergy* 75 (5) (2020) 1023–1042, <https://doi.org/10.1111/all.14221>.
- [27] I. Agache, C.A. Akdis, M. Akdis, et al., EAAACI biologicals guidelines—recommendations for severe asthma, *Allergy* 76 (1) (2021) 14–44, <https://doi.org/10.1111/all.14425>.
- [28] A. Akenroye, G. Lassiter, J.W. Jackson, et al., Comparative efficacy of mepolizumab, benralizumab, and dupilumab in eosinophilic asthma: a Bayesian network meta-analysis, *J. Allergy Clin. Immunol.* 150 (5) (2022) 1097–1105.e12, <https://doi.org/10.1016/j.jaci.2022.05.024>.
- [29] H. Ahmed, S. Turner, Severe asthma in children—a review of definitions, epidemiology, and treatment options in 2019, *Pediatr. Pulmonol.* 54 (6) (2019) 778–787, <https://doi.org/10.1002/ppul.24317>.
- [30] M. Forero Molina, W. Okoniewski, S. Puranik, et al., Severe asthma in children: description of a large multidisciplinary clinical cohort, *Pediatr. Pulmonol.* 57 (6) (2022) 1447–1455, <https://doi.org/10.1002/ppul.25887>.
- [31] L. Ronco, A. Folino, M. Goia, B. Crida, I. Esposito, E. Bignamini, Do not forget asthma comorbidities in pediatric severe asthma, *Front Pediatr* 10 (2022), 932366, <https://doi.org/10.3389/fped.2022.932366>.
- [32] C. Caruso, S. Colantuono, S. Arasi, et al., Heterogeneous condition of asthmatic children patients: a narrative review, *Children* 9 (3) (2022) 332, <https://doi.org/10.3390/children9030332>.
- [33] A. Bush, How to choose the correct drug in severe pediatric asthma, *Front Pediatr* 10 (2022), 902168, <https://doi.org/10.3389/fped.2022.902168>.
- [34] J. Just, A. Deschildre, S. Lejeune, F. Amat, New perspectives of childhood asthma treatment with biologics, in: P. Eigenmann (Ed.), *Pediatr Allergy Immunol*, 2018, <https://doi.org/10.1111/pai.13007>. Published online December 16.
- [35] L.B. Bacharier, D.J. Jackson, Biologics in the treatment of asthma in children and adolescents, Published online January 24, *J. Allergy Clin. Immunol.* (2023), <https://doi.org/10.1016/j.jaci.2023.01.002>. S0091-6749(23)00006-4.
- [36] E.P. Perikleous, P. Steiropoulos, E. Nena, E. Paraskakis, Biologic therapies in pediatric asthma, *J. Personalized Med.* 12 (6) (2022) 999, <https://doi.org/10.3390/jpm12060999>.
- [37] A. Nopp, S.G.O. Johansson, J. Adéoyin, J. Ankerst, M. Palmqvist, H. Oman, After 6 years with Xolair; a 3-year withdrawal follow-up, *Allergy* 65 (1) (2010) 56–60, <https://doi.org/10.1111/j.1398-9995.2009.02144.x>.
- [38] M.D.C. Vennera, C. Sabadell, C. Picado, Spanish Omalizumab Registry, Duration of the efficacy of omalizumab after treatment discontinuation in “real life” severe asthma, *Thorax* 73 (8) (2018) 782–784, <https://doi.org/10.1136/thoraxjnl-2017-210017>.
- [39] M. Molimard, L. Mala, I. Bourdeix, V. Le Gros, Observational study in severe asthmatic patients after discontinuation of omalizumab for good asthma control, *Respir. Med.* 108 (4) (2014) 571–576, <https://doi.org/10.1016/j.rmed.2014.02.003>.
- [40] P. Flood-Page, C. Swenson, I. Faiferman, et al., A study to evaluate safety and efficacy of mepolizumab in patients with moderate persistent asthma, *Am. J. Respir. Crit. Care Med.* 176 (11) (2007) 1062–1071, <https://doi.org/10.1164/rccm.200701-085OC>.
- [41] J. Bousquet, K. Rabe, M. Humbert, et al., Predicting and evaluating response to omalizumab in patients with severe allergic asthma, *Respir. Med.* 101 (7) (2007) 1483–1492, <https://doi.org/10.1016/j.rmed.2007.01.011>.
- [42] D.B. Price, A. Rigazio, J.D. Campbell, et al., Blood eosinophil count and prospective annual asthma disease burden: a UK cohort study, *Lancet Respir. Med.* 3 (11) (2015) 849–858, [https://doi.org/10.1016/S2213-2600\(15\)00367-7](https://doi.org/10.1016/S2213-2600(15)00367-7).
- [43] F.N. Schleich, A. Chevreton, V. Paulus, et al., Importance of concomitant local and systemic eosinophilia in uncontrolled asthma, *Eur. Respir. J.* 44 (1) (2014) 97–108, <https://doi.org/10.1183/09031936.00201813>.
- [44] P. Nair, Predictors of response to anti-IL-5 biologics, *Respirology* 25 (11) (2020) 1123–1125, <https://doi.org/10.1111/resp.13926>.
- [45] F. Abbas, S. Georas, X. Cai, S. Khurana, Asthma biologics, *Ann. Allergy Asthma Immunol.* 127 (6) (2021) 655–660.e1, <https://doi.org/10.1016/j.ana.2021.08.416>.
- [46] J.M. Escamilla-Gil, M. Fernandez-Nieto, N. Acevedo, Understanding the cellular sources of the fractional exhaled nitric oxide (FeNO) and its role as a biomarker of type 2 inflammation in asthma, *BioMed Res. Int.* 2022 (2022), 5753524, <https://doi.org/10.1155/2022/5753524>.
- [47] R. Shrimanker, O. Keene, G. Hynes, S. Wenzel, S. Yancey, I.D. Pavord, Prognostic and predictive value of blood eosinophil count, fractional exhaled nitric oxide, and their combination in severe asthma: a post hoc analysis, *Am. J. Respir. Crit. Care Med.* 200 (10) (2019) 1308–1312, <https://doi.org/10.1164/rccm.201903-0599LE>.
- [48] C. Pellaia, G. Paoletti, F. Puggioni, et al., Interleukin-5 in the pathophysiology of severe asthma, *Front. Physiol.* 10 (2019) 1514, <https://doi.org/10.3389/fphys.2019.01514>.
- [49] A.P. Hearn, J. Kavanagh, G. d’Ancona, et al., The relationship between FeNO and effectiveness of mepolizumab and benralizumab in severe eosinophilic asthma, *J. Allergy Clin. Immunol. Pract.* 9 (5) (2021) 2093–2096.e1, <https://doi.org/10.1016/j.jaip.2021.01.008>.
- [50] C. Menigoz, S. Dirou, A. Chambellan, et al., Use of FeNO to predict anti-IL-5 and IL-5R biologics efficacy in a real-world cohort of adults with severe eosinophilic asthma, *J. Asthma* (2022) 1–9, <https://doi.org/10.1080/02770903.2022.2136526>. Published online November 15.
- [51] I.D. Pavord, Y. Deniz, J. Corren, et al., Baseline FeNO independently predicts the dupilumab response in patients with moderate-to-severe asthma, Published online December, *J. Allergy Clin. Immunol. Pract.* (2022), <https://doi.org/10.1016/j.jaip.2022.11.043>. S2213219822013034.
- [52] J. Corren, T.H. Pham, E. Garcia Gil, et al., Baseline type 2 biomarker levels and response to tezepelumab in severe asthma, *Allergy* 77 (6) (2022) 1786–1796, <https://doi.org/10.1111/all.15197>.
- [53] S. Couillard, I.D. Pavord, L.G. Heaney, N. Petousi, T.S.C. Hinks, Sub-stratification of type-2 high airway disease for therapeutic decision-making: a ‘bomb’ (blood eosinophils) meets ‘magnet’ (FeNO) framework, *Respirology* 27 (8) (2022) 573–577, <https://doi.org/10.1111/resp.14294>.
- [54] X.C. Wan, P.G. Woodruff, Biomarkers in severe asthma, *Immunol. Allergy Clin. 36* (3) (2016) 547.
- [55] E. Wang, M.E. Wechsler, A rational approach to compare and select biologic therapeutics in asthma, *Ann Allergy Asthma Immunol Off Publ Am Coll Allergy Asthma Immunol* 128 (4) (2022) 379–389, <https://doi.org/10.1016/j.anaai.2022.01.024>.
- [56] M.E. Wechsler, L.B. Ford, J.F. Maspero, et al., Long-term safety and efficacy of dupilumab in patients with moderate-to-severe asthma (TRAVERSE): an open-label extension study, *Lancet Respir. Med.* 10 (1) (2022) 11–25, [https://doi.org/10.1016/S2213-2600\(21\)00322-2](https://doi.org/10.1016/S2213-2600(21)00322-2).
- [57] D. Narendra, J. Blixt, N.A. Hanania, Immunological biomarkers in severe asthma, *Semin. Immunol.* 46 (2019), 101332, <https://doi.org/10.1016/j.smim.2019.101332>.
- [58] Z. Diamant, S. Vijverberg, K. Alving, et al., Toward clinically applicable biomarkers for asthma: an EAACI position paper, *Allergy* 74 (10) (2019) 1835–1851, <https://doi.org/10.1111/all.13806>.
- [59] I. Striz, K. Golebski, Z. Strizova, et al., New insights into the pathophysiology and therapeutic targets of asthma and comorbid chronic rhinosinusitis with or without nasal polyposis, *Clin Sci Lond Engl* 137 (9) (2023) 727–753, <https://doi.org/10.1042/CS20190281>, 1979.
- [60] D.E. Shaw, A.R. Sousa, S.J. Fowler, et al., Clinical and inflammatory characteristics of the European U-BIOPRED adult severe asthma cohort, *Eur. Respir. J.* 46 (5) (2015) 1308–1321, <https://doi.org/10.1183/13993003.00779-2015>.
- [61] C. Bachert, J.K. Han, M. Desrosiers, et al., Efficacy and safety of dupilumab in patients with severe chronic rhinosinusitis with nasal polyps (LIBERTY NP SINUS-24 and LIBERTY NP SINUS-52): results from two multicentre, randomised, double-blind, placebo-controlled, parallel-group phase 3 trials, *Lancet Lond Engl* 394 (10209) (2019) 1638–1650, [https://doi.org/10.1016/S0140-6736\(19\)31881-1](https://doi.org/10.1016/S0140-6736(19)31881-1).
- [62] P. Gevaert, T.A. Omachi, J. Corren, et al., Efficacy and safety of omalizumab in nasal polyposis: 2 randomized phase 3 trials, *J. Allergy Clin. Immunol.* 146 (3) (2020) 595–605, <https://doi.org/10.1016/j.jaci.2020.05.032>.
- [63] J.K. Han, C. Bachert, W. Fokkens, et al., Mepolizumab for chronic rhinosinusitis with nasal polyps (SYNAPSE): a randomised, double-blind, placebo-controlled, phase 3 trial, *Lancet Respir. Med.* 9 (10) (2021) 1141–1153, [https://doi.org/10.1016/S2213-2600\(21\)00097-7](https://doi.org/10.1016/S2213-2600(21)00097-7).
- [64] A.D. Workman, M.A. Kohanski, N.A. Cohen, Biomarkers in chronic rhinosinusitis with nasal polyps, *Immunol. Allergy Clin.* 38 (4) (2018) 679–692, <https://doi.org/10.1016/j.iac.2018.06.006>.
- [65] A. Bakakos, F. Schleich, P. Bakakos, Biological therapy of severe asthma and nasal polyps, *J. Personalized Med.* 12 (6) (2022) 976, <https://doi.org/10.3390/jpm12060976>.
- [66] E.L. Simpson, T. Bieber, E. Guttman-Yassky, et al., Two phase 3 trials of dupilumab versus placebo in atopic dermatitis, *N. Engl. J. Med.* 375 (24) (2016) 2335–2348, <https://doi.org/10.1056/NEJMoa1610020>.
- [67] M.E. Rothenberg, Scientific journey to the first FDA-approved drug for eosinophilic esophagitis, *J. Allergy Clin. Immunol.* 150 (6) (2022) 1325–1332, <https://doi.org/10.1016/j.jaci.2022.09.027>.
- [68] G. Yosipovitch, Dupilumab Significantly Improves Itch and Skin Lesions in Patients with Prurigo Nodularis: Results from a 2nd Phase 3 Trial (LIBERTY-PN PRIME), 2022. Published online. (Accessed 1 September 2022).
- [69] M.E. Wechsler, P. Akuthota, D. Jayne, et al., Mepolizumab or placebo for eosinophilic granulomatosis with polyangiitis, *N. Engl. J. Med.* 376 (20) (2017) 1921–1932, <https://doi.org/10.1056/NEJMoa1702079>.
- [70] F. Roufosse, J.E. Kahn, M.E. Rothenberg, et al., Efficacy and safety of mepolizumab in hypereosinophilic syndrome: a phase III, randomized, placebo-controlled trial, *J. Allergy Clin. Immunol.* 146 (6) (2020) 1397–1405, <https://doi.org/10.1016/j.jaci.2020.08.037>.
- [71] J. White, S. Dubey, Eosinophilic granulomatosis with polyangiitis: a review, *Autoimmun. Rev.* 22 (1) (2023), 103219, <https://doi.org/10.1016/j.autrev.2022.103219>.
- [72] E.H. Bel, S.E. Wenzel, P.J. Thompson, et al., Oral glucocorticoid-sparing effect of mepolizumab in eosinophilic asthma, *N. Engl. J. Med.* 371 (13) (2014) 1189–1197, <https://doi.org/10.1056/NEJMoa1403291>.
- [73] P. Nair, S. Wenzel, K.F. Rabe, et al., Oral glucocorticoid-sparing effect of benralizumab in severe asthma, *N. Engl. J. Med.* 376 (25) (2017) 2448–2458, <https://doi.org/10.1056/NEJMoa1703501>.
- [74] Prescribing information dupilumab. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/7610551bl.pdf. (Accessed 25 February 2023).
- [75] M.E. Wechsler, A. Menzies-Gow, C.E. Brightling, et al., Evaluation of the oral corticosteroid-sparing effect of tezepelumab in adults with oral corticosteroid-dependent asthma (SOURCE): a randomised, placebo-controlled, phase 3 study, *Lancet Respir. Med.* 10 (7) (2022) 650–660, [https://doi.org/10.1016/S2213-2600\(21\)00537-3](https://doi.org/10.1016/S2213-2600(21)00537-3).
- [76] Prescribing information-mepolizumab. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/761122s008,125526s0191bl.pdf. (Accessed 25 February 2023).

- [77] United States Food and Drug Administration, Prescribing information benralizumab. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/761070s000lbl.pdf. (Accessed 25 February 2023).
- [78] Prescribing information tezepelumab. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/761224s000lbl.pdf. (Accessed 25 February 2023).
- [79] Prescribing information reslizumab. https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/761033lbl.pdf. (Accessed 25 February 2023).
- [80] Prescribing information omalizumab. https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/103976s5225lbl.pdf. (Accessed 25 February 2023).
- [81] J.W. Inselman, M.M. Jeffery, J.T. Maddux, N.D. Shah, M.A. Rank, Trends and disparities in asthma biologic use in the United States, *J. Allergy Clin. Immunol. Pract.* 8 (2) (2020) 549–554.e1, <https://doi.org/10.1016/j.jaip.2019.08.024>.
- [82] Shared decision making tool for severe asthma. <https://asthma.chestnet.org/sdm-tool/>. (Accessed 26 February 2023). <https://allergyasthmanetwork.org/health-a-z/shared-decision-making/>.
- [83] G. Rejñó, C. Lundholm, T. Gong, K. Larsson, S. Saltvedt, C. Almqvist, Asthma during pregnancy in a population-based study - pregnancy complications and adverse perinatal outcomes, 8, in: K. Laine (Ed.), *PLoS ONE*, vol. 9, 2014, e104755, <https://doi.org/10.1371/journal.pone.0104755>.
- [84] J.A. Namazy, L. Blais, E.B. Andrews, et al., Pregnancy outcomes in the omalizumab pregnancy registry and a disease-matched comparator cohort, *J. Allergy Clin. Immunol.* 145 (2) (2020) 528–536.e1, <https://doi.org/10.1016/j.jaci.2019.05.019>.
- [85] R. Khamisy-Farah, G. Damiani, J.D. Kong, J.H. Wu, N.L. Bragazzi, Safety profile of Dupilumab during pregnancy: a data mining and disproportionality analysis of over 37,000 reports from the WHO individual case safety reporting database (VigiBase™), *Eur. Rev. Med. Pharmacol. Sci.* 25 (17) (2021) 5448–5451, <https://doi.org/10.26355/eurrev.202109.26652>.
- [86] B. Pfaller, J. José Yepes-Núñez, I. Agache, et al., Biologicals in atopic disease in pregnancy: an EAACI position paper, *Allergy* 76 (1) (2021) 71–89, <https://doi.org/10.1111/all.14282>.
- [87] M. Morten, A. Collison, V.E. Murphy, et al., Managing Asthma in Pregnancy (MAP) trial: FENO levels and childhood asthma, *J. Allergy Clin. Immunol.* 142 (6) (2018) 1765–1772.e4, <https://doi.org/10.1016/j.jaci.2018.02.039>.
- [88] J.J.M.H. van Bragt, I.M. Adcock, E.H.D. Bel, et al., Characteristics and treatment regimens across ERS SHARP severe asthma registries, *Eur. Respir. J.* 55 (1) (2020), 1901163, <https://doi.org/10.1183/13993003.01163-2019>.
- [89] A.N. Menzies-Gow, C. McBrien, B. Unni, et al., Real world biologic use and switch patterns in severe asthma: data from the international severe asthma registry and the US CHRONICLE study, *J. Asthma Allergy* 15 (2022) 63–78, <https://doi.org/10.2147/JAA.S328653>.
- [90] E. Khaleva, A. Rattu, C. Brightling, et al., Definitions of non-response and response to biological therapy for severe asthma: a systematic review, *ERJ Open Res* 9 (3) (2023), <https://doi.org/10.1183/23120541.00444-2022>, 00444-02022.
- [91] N.A. Hanania, M. Castro, E. Bateman, et al., Efficacy of dupilumab in patients with moderate-to-severe asthma and persistent airflow obstruction, *Ann Allergy Asthma Immunol Off Publ Am Coll Allergy Asthma Immunol* 130 (2) (2023) 206–214.e2, <https://doi.org/10.1016/j.ana.2022.10.018>.
- [92] GINA, Difficult-to-Treat and Severe Asthma in Adolescent and Adult Patients: Diagnosis and Management, May 2022. V4.0, www.ginasthma.org. (Accessed 14 August 2023).
- [93] J.W. Upham, C. Le Lievre, D.J. Jackson, et al., Defining a severe asthma super-responder: findings from a Delphi process, *J. Allergy Clin. Immunol. Pract.* 9 (11) (2021) 3997–4004, <https://doi.org/10.1016/j.jaip.2021.06.041>.
- [94] K.R. Chapman, F.C. Albers, B. Chippis, et al., The clinical benefit of mepolizumab replacing omalizumab in uncontrolled severe eosinophilic asthma, *Allergy* 74 (9) (2019) 1716–1726, <https://doi.org/10.1111/all.13850>.
- [95] G.E. Carpagnano, C. Pelaia, M. D'Amato, et al., Switching from omalizumab to mepolizumab: real-life experience from Southern Italy, *Ther. Adv. Respir. Dis.* 14 (2020), 1753466620929231, <https://doi.org/10.1177/1753466620929231>.
- [96] H. Nagase, M. Suzukawa, K. Oishi, K. Matsunaga, Biologics for severe asthma: the real-world evidence, effectiveness of switching, and prediction factors for the efficacy, *Allergol. Int.* 72 (1) (2023) 11–23, <https://doi.org/10.1016/j.alit.2022.11.008>.
- [97] M. Lommatzsch, H. Suhling, S. Korn, et al., Safety of combining biologics in severe asthma: asthma-related and unrelated combinations, *Allergy* (2022), <https://doi.org/10.1111/all.15379>. Published online May 18.
- [98] J.A. Singh, C. Cameron, S. Noorbaloochi, et al., Risk of serious infection in biological treatment of patients with rheumatoid arthritis: a systematic review and meta-analysis, *Lancet Lond Engl* 386 (9990) (2015) 258–265, [https://doi.org/10.1016/S0140-6736\(14\)61704-9](https://doi.org/10.1016/S0140-6736(14)61704-9).
- [99] M.E. Wechsler, M.K. Ruddy, I.D. Pavord, et al., Efficacy and safety of Itepekimab in patients with moderate-to-severe asthma, *N. Engl. J. Med.* 385 (18) (2021) 1656–1668, <https://doi.org/10.1056/NEJMoA2024257>.
- [100] A.N. Frix, L.G. Heaney, B. Dahlén, et al., Heterogeneity in the use of biologics for severe asthma in Europe: a SHARP ERS study, *ERJ Open Res* 8 (4) (2022), <https://doi.org/10.1183/23120541.00273-2022>, 00273-02022.
- [101] C. Venegas Garrido, M. Mukherjee, A. Bhalla, P. Nair, Airway autoimmunity, asthma exacerbations, and response to biologics, *Clin. Exp. Allergy* 52 (12) (2022) 1365–1378, <https://doi.org/10.1111/cea.14220>.
- [102] K.M. MacDonald, A. Kavati, B. Ortiz, A. Alhossan, C.S. Lee, I. Abraham, Short- and long-term real-world effectiveness of omalizumab in severe allergic asthma: systematic review of 42 studies published 2008–2018, *Expert Rev. Clin. Immunol.* 15 (5) (2019) 553–569, <https://doi.org/10.1080/1744666X.2019.1574571>.
- [103] N.A. Hanania, R. Niven, P. Chanez, et al., Long-term effectiveness and safety of omalizumab in pediatric and adult patients with moderate-to-severe inadequately controlled allergic asthma, *World Allergy Organ J* 15 (10) (2022), 100695, <https://doi.org/10.1016/j.waojou.2022.100695>.
- [104] N. Lugogo, C. Domingo, P. Chanez, et al., Long-term efficacy and safety of mepolizumab in patients with severe eosinophilic asthma: a multi-center, open-label, phase IIIb study, *Clin. Therapeut.* 38 (9) (2016) 2058–2070.e1, <https://doi.org/10.1016/j.clinthera.2016.07.010>.
- [105] S. Khurana, G.G. Brusselle, E.H. Bel, et al., Long-term safety and clinical benefit of mepolizumab in patients with the most severe eosinophilic asthma: the COSMEX study, *Clin. Therapeut.* 41 (10) (2019) 2041–2056.e5, <https://doi.org/10.1016/j.clinthera.2019.07.007>.
- [106] S. Khatri, W. Moore, P.G. Gibson, et al., Assessment of the long-term safety of mepolizumab and durability of clinical response in patients with severe eosinophilic asthma, *J. Allergy Clin. Immunol.* 143 (5) (2019) 1742–1751.e7, <https://doi.org/10.1016/j.jaci.2018.09.033>.
- [107] W.W. Busse, E.R. Bleecker, J.M. FitzGerald, et al., Long-term safety and efficacy of benralizumab in patients with severe, uncontrolled asthma: 1-year results from the BORA phase 3 extension trial, *Lancet Respir. Med.* 7 (1) (2019) 46–59, [https://doi.org/10.1016/S2213-2600\(18\)30406-5](https://doi.org/10.1016/S2213-2600(18)30406-5).
- [108] L.D. Tan, B. Schaeffer, A. Alisma, Parasitic (helminthic) infection while on asthma biologic treatment: not everything is what it seems, *J. Asthma Allergy* 12 (2019) 415–420, <https://doi.org/10.2147/JAA.S223402>.
- [109] M.E. Wechsler, A.D. Klion, P. Paggiaro, et al., Effect of dupilumab on blood eosinophil counts in patients with asthma, chronic rhinosinusitis with nasal polyps, atopic dermatitis, or eosinophilic esophagitis, *J. Allergy Clin. Immunol. Pract.* 10 (10) (2022) 2695–2709, <https://doi.org/10.1016/j.jaip.2022.05.019>.
- [110] K. Eger, L. Pet, E.J.M. Weersink, E.H. Bel, Complications of switching from anti-IL-5 or anti-IL-5R to dupilumab in corticosteroid-dependent severe asthma, *J. Allergy Clin. Immunol. Pract.* 9 (7) (2021) 2913–2915, <https://doi.org/10.1016/j.jaip.2021.02.042>.
- [111] I. Briegel, A. Felicio-Briegel, P. Mertsch, N. Kneidinger, F. Haubner, K. Milger, Hypereosinophilia with systemic manifestations under dupilumab and possibility of dual benralizumab and dupilumab therapy in patients with asthma and CRSwNP, *J. Allergy Clin. Immunol. Pract.* 9 (12) (2021) 4477–4479, <https://doi.org/10.1016/j.jaip.2021.07.049>.
- [112] C. Dupin, D. Belhadi, L. Guilleminault, et al., Effectiveness and safety of dupilumab for the treatment of severe asthma in a real-life French multi-centre adult cohort, *Clin Exp Allergy J Br Soc Allergy Clin Immunol* 50 (7) (2020) 789–798, <https://doi.org/10.1111/cea.13614>.
- [113] A. Menzies-Gow, M.E. Wechsler, C.E. Brightling, et al., Long-term safety and efficacy of tezepelumab in people with severe, uncontrolled asthma (DESTINATION): a randomised, placebo-controlled extension study, *Lancet Respir. Med.* 11 (5) (2023) 425–438, [https://doi.org/10.1016/S2213-2600\(22\)00492-1](https://doi.org/10.1016/S2213-2600(22)00492-1).
- [114] J. Bousquet, M. Humbert, P.G. Gibson, et al., Real-world effectiveness of omalizumab in severe allergic asthma: a meta-analysis of observational studies, *J. Allergy Clin. Immunol. Pract.* 9 (7) (2021) 2702–2714, <https://doi.org/10.1016/j.jaip.2021.01.011>.
- [115] C. Pilette, G.W. Canonica, R. Chaudhuri, et al., REALITI-A study: real-world oral corticosteroid-sparing effect of mepolizumab in severe asthma, Published online, *J. Allergy Clin. Immunol. Pract.* (June 2022), <https://doi.org/10.1016/j.jaip.2022.05.042>, S2213219822006298.
- [116] T. Harrison, G.W. Canonica, G. Chupp, et al., Real-world mepolizumab in the prospective severe asthma REALITI-A study: initial analysis, *Eur. Respir. J.* 56 (4) (2020), 2000151, <https://doi.org/10.1183/13993003.00151-2020>.
- [117] Y. Chung, R. Katial, F. Mu, et al., Real-world effectiveness of benralizumab: results from the ZEPHYR 1 study, *Ann Allergy Asthma Immunol Off Publ Am Coll Allergy Asthma Immunol* 128 (6) (2022) 669–676.e6, <https://doi.org/10.1016/j.ana.2022.02.017>.
- [118] J.E. Kavanagh, A.P. Hearn, J. Dhariwal, et al., Real-world effectiveness of benralizumab in severe eosinophilic asthma, *Chest* 159 (2) (2021) 496–506, <https://doi.org/10.1016/j.chest.2020.08.2083>.
- [119] J.C. Thelen, C.M. van Zelst, S.E. van Brummelen, et al., Efficacy and safety of dupilumab as add-on therapy for patients with severe asthma: a real-world Dutch cohort study, *Respir. Med.* 206 (2023), 107058, <https://doi.org/10.1016/j.rmed.2022.107058>.
- [120] A. Menzies-Gow, M. Bafadhel, W.W. Busse, et al., An expert consensus framework for asthma remission as a treatment goal, *J. Allergy Clin. Immunol.* 145 (3) (2020) 757–765, <https://doi.org/10.1016/j.jaci.2019.12.006>.
- [121] L. Pérez de Llano, I. Dávila, E. Martínez-Moragón, et al., Development of a tool to measure the clinical response to biologic therapy in uncontrolled severe asthma: the FEV1, exacerbations, oral corticosteroids, symptoms score, *J. Allergy Clin. Immunol. Pract.* 9 (7) (2021) 2725–2731, <https://doi.org/10.1016/j.jaip.2021.01.033>.
- [122] G.W. Canonica, F. Blasi, G.E. Carpagnano, et al., SANI definition of clinical remission in severe asthma: a Delphi consensus, Published online, *J. Allergy Clin. Immunol. Pract.* (August 2023), <https://doi.org/10.1016/j.jaip.2023.07.041>, S2213219823008164.
- [123] A. Portacci, I. Iorillo, V.N. Quaranta, et al., Severe asthma clinical remission after biologic treatment with anti-IL4/IL13: a real-life experience, *Respir. Med.* 217 (2023), 107348, <https://doi.org/10.1016/j.rmed.2023.107348>.
- [124] G. Varricchi, S. Ferri, J. Pepys, et al., Biologics and airway remodeling in severe asthma, *Allergy* 77 (12) (2022) 3538–3552, <https://doi.org/10.1111/all.15473>.
- [125] G. Kardas, P. Kuna, M. Panek, Biological therapies of severe asthma and their possible effects on airway remodeling, *Front. Immunol.* 11 (2020) 1134, <https://doi.org/10.3389/fimmu.2020.01134>.

- [126] P.J. Niedbalski, J. Choi, C.S. Hall, M. Castro, Imaging in asthma management, *Semin. Respir. Crit. Care Med.* (2022), <https://doi.org/10.1055/s-0042-1743289>. Published online February 24.
- [127] S. Svenningsen, E. Haider, C. Boylan, et al., CT and functional MRI to evaluate airway mucus in severe asthma, *Chest* 155 (6) (2019) 1178–1189, <https://doi.org/10.1016/j.chest.2019.02.403>.
- [128] E. Pompe, A.K.A.L. Kwee, V. Tejwani, T. Siddharthan, F.A.A. Mohamed Hoesin, Imaging-derived biomarkers in Asthma: current status and future perspectives, *Respir. Med.* 208 (2023), 107130, <https://doi.org/10.1016/j.rmed.2023.107130>.
- [129] K. Hamada, K. Oishi, Y. Murata, T. Hirano, K. Matsunaga, Feasibility of discontinuing biologics in severe asthma: an algorithmic approach, *J. Asthma Allergy* 14 (2021) 1463–1471, <https://doi.org/10.2147/JAA.S340684>.
- [130] M.M. Jeffery, J.W. Inselman, J.T. Maddux, R.W. Lam, N.D. Shah, M.A. Rank, Asthma patients who stop asthma biologics have a similar risk of asthma exacerbations as those who continue asthma biologics, *J. Allergy Clin. Immunol. Pract.* 9 (7) (2021) 2742–2750.e1, <https://doi.org/10.1016/j.jaip.2021.02.031>.
- [131] A.S. Larkin, S.E. Wenzel, Precision medicine in pediatric severe asthma: targeted blockade of type 2 inflammation, *Cell Rep Med* 3 (3) (2022), 100570, <https://doi.org/10.1016/j.xcrm.2022.100570>.
- [132] K. Gadkar, J. Feigelman, S. Sukumaran, et al., Integrated systems modeling of severe asthma: exploration of IL -33/ST2 antagonism, *CPT Pharmacometrics Syst. Pharmacol.* 11 (9) (2022) 1268–1277, <https://doi.org/10.1002/psp4.12842>.
- [133] B. Esty, H. Harb, L.M. Bartnikas, et al., Treatment of severe persistent asthma with IL-6 receptor blockade, *J. Allergy Clin. Immunol. Pract.* 7 (5) (2019) 1639–1642.e4, <https://doi.org/10.1016/j.jaip.2019.02.043>.
- [134] M. Croft, T. So, W. Duan, P. Soroosh, The significance of OX40 and OX40L to T-cell biology and immune disease, *Immunol. Rev.* 229 (1) (2009) 173–191, <https://doi.org/10.1111/j.1600-065X.2009.00766.x>.
- [135] R. Normansell, S. Walker, S.J. Milan, E.H. Walters, P. Nair, Omalizumab for asthma in adults and children, *Cochrane Database Syst. Rev.* 1 (2014), <https://doi.org/10.1002/14651858.CD003559.pub4>. CD003559.
- [136] I.D. Pavord, S. Korn, P. Howarth, et al., Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial, *Lancet* 380 (9842) (2012) 651–659, [https://doi.org/10.1016/S0140-6736\(12\)60988-X](https://doi.org/10.1016/S0140-6736(12)60988-X).
- [137] A. Gupta, M. Ikeda, B. Geng, et al., Long-term safety and pharmacodynamics of mepolizumab in children with severe asthma with an eosinophilic phenotype, *J. Allergy Clin. Immunol.* 144 (5) (2019) 1336–1342.e7, <https://doi.org/10.1016/j.jaci.2019.08.005>.
- [138] G. Ferrante, L. Tenero, M. Piazza, G. Piacentini, Severe pediatric asthma therapy: dupilumab, *Front Pediatr* 10 (2022), 963610, <https://doi.org/10.3389/fped.2022.963610>.
- [139] N. Ullmann, F. Peri, O. Florio, et al., Severe pediatric asthma therapy: mepolizumab, *Front Pediatr* 10 (2022), 920066, <https://doi.org/10.3389/fped.2022.920066>.