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Biologic treatment eligibility for real-world patients with severe asthma: The IDEAL study

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ABSTRACT

Objectives: Severe asthma comprises several distinct phenotypes. Consequently, patients with severe asthma can be eligible for more than one biologic treatment targeting Th2 inflammation, such as anti-interleukin (IL)-5 and anti-immunoglobulin (Ig) E. The objective of this study was to describe treatment eligibility and overlap in treatment eligibility for mepolizumab (anti-IL-5), omalizumab (anti-IgE) and reslizumab (anti-IL-5) in patients with severe asthma, who were recruited from clinical practice. **Methods:** This cross-sectional, single-visit, observational study in six countries enrolled patients with severe asthma (defined by American Thoracic Society/European Respiratory Society guidelines). Assessable patients were analysed as a total cohort and a sub-cohort, who were not currently receiving omalizumab. Treatment eligibility was defined according to the local prescribing information or protocol-defined inclusion/exclusion criteria. Patients currently receiving omalizumab were automatically categorised as omalizumab-eligible. **Results:** The total cohort comprised 670 patients who met the analysis criteria, of whom 20% were eligible for mepolizumab, 31–41% were eligible for omalizumab (depending on eligibility criteria used), and 5% were eligible for reslizumab. In patients not currently receiving omalizumab ($n = 502$), proportions eligible for each biologic were similar (mepolizumab: 20%, reslizumab 6%) or lower (omalizumab 7–21%) than those for the total cohort. Overlap in treatment eligibility varied; in mepolizumab-eligible patients not currently receiving omalizumab ($n = 101$), 27–37% were omalizumab-eligible and 18% were reslizumab-eligible. **Conclusions:** Treatment eligibility for mepolizumab and omalizumab was higher than that for reslizumab. Although there was some overlap in treatment eligibility, the patient groups eligible for treatment with anti-IL-5 or anti-IgE therapies were often distinct, emphasising the different phenotypes and endotypes in severe asthma.

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Introduction

Of approximately 242 million people worldwide with asthma, 5–10% have severe asthma [1, 2]. For many patients, asthma can be managed with the use of inhaled corticosteroids (ICS), and further intensified with the addition of a long-acting β_2 -agonist (LABA) to attain control [2, 3]. In severe asthma, high-dose ICS may be combined with an additional controller or oral corticosteroids (OCSs) [2]. In spite of these intensified measures, a subset of patients with severe asthma continue to have uncontrolled disease, characterised by frequent symptoms, continued exacerbations, persistent impaired lung function, and reduced health-related quality of life (HRQoL) [2].

For severe asthma, phenotypes are heterogeneous with respect to clinical characteristics, physiological measures and biomarker expression [4–6]. Two clinically recognised phenotypes include severe allergic asthma and severe eosinophilic asthma [2]. Allergic asthma is characterised by high serum immunoglobulin (Ig) E, high exhaled nitric oxide (FeNO) and eosinophilic inflammation, while eosinophilic asthma is characterised by eosinophilic inflammation, recurrent exacerbations and high FeNO [2]. Due to the significant unmet medical need, biologic therapies aiming to reduce the rate of exacerbations are emerging, targeting different immunologic mediators of severe asthma [7].

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Three monoclonal antibody-based therapies that target immunologic mediators common in specific severe asthma phenotypes are now available: omalizumab (Genentech, Inc., South San Francisco, CA), mepolizumab (GSK, London, UK), and reslizumab (Teva, Jerusalem, Israel). Omalizumab is a monoclonal anti-IgE antibody for patients with moderate-to-severe allergic asthma [8, 9], while mepolizumab and reslizumab are monoclonal anti-IL-5 antibody treatments for patients with severe eosinophilic asthma [10–12].

In clinical practice, patients may present with overlapping phenotypic characteristics making them eligible for treatments, which either neutralise IL-5 (reducing peripheral and tissue eosinophils) or reduce levels of IgE (targeting the allergic component), or both. The relative sizes of the populations eligible for treatment with anti-IL-5, anti-IgE or both (the overlap population) are poorly understood.

The objective of this study was to describe, in a population of patients with severe asthma, the proportion of patients with eligibility for one or more of mepolizumab, omalizumab and reslizumab. This was assessed in a cross-sectional cohort of patients recruited from routine clinical practice to provide a real-world reflection of the severe asthma population. A subgroup analysis was also performed in patients not currently prescribed any biologic treatment. It was assumed that these patients would represent the patients potentially eligible for initiating treatment with any of the currently available biologic treatments in clinical practice.

Methods

Study design

IDEAL (Identification and Description of sEvere Asthma patients in a cross-sectionaL study; 201722, NCT02293265) was an observational cohort study that recruited patients with severe asthma in a variety of clinical settings, including allergists, pulmonologists and primary care clinics, across six countries (Australia, Canada, France, Germany, the UK and USA) between December 8, 2014 and May 1, 2015.

The study was conducted in accordance with the International Conference on Harmonisation Good Clinical Practice standards and the ethical principles outlined in the Declaration of Helsinki. Ethical approval was obtained from a national, regional or investigational centre ethics committee or institutional review board, according to all applicable country-specific requirements. All patients (or their legal guardians) provided written informed consent prior to study participation.

Patients

To ensure a population representative of real-world patients, only a small number of selection criteria were applied. Patients enrolled were ≥ 12 years of age, with severe asthma defined according to American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines (asthma requiring high-dose ICS plus at least one of the following additional controller[s] for ≥ 12 months [Global Initiative for Asthma Step 4/5]: LABA, leukotriene modifier, theophylline, or continuous or near continuous OCS [i.e., maintenance OCS for $\geq 50\%$ of the previous year]) [2]. If a patient was on a fixed-dose combination medication, then the maximum recommended dose of the ICS/LABA combination per local label was acceptable for fulfilling the severe asthma criteria. No medications were prohibited. Patients were excluded if they had participated in an interventional clinical trial for asthma within the past 12 months.

Study visits and assessments

The study had a maximum of two visits, Visit 0 (screening) and Visit 1 (assessments). Visit 1 could occur on the same day as screening and it was recommended to be completed within 14 days of Visit 0 (if the patient did not have a history of pulmonary function test or reversibility test in their medical records during the prior 12-month period).

At screening, the most recent assessment data for the following parameters were obtained from the patients' medical records for the prior 12 months: airway reversibility test (indicating a response of $\geq 12\%$ and 200 mL in forced expiratory volume in 1 second [FEV₁] to short-acting β_2 -agonist [SABA] administration); spirometry (pre- and post-bronchodilator FEV₁ and FEV₁/forced vital capacity [FVC]); asthma exacerbation history (exacerbations defined as requiring treatment with OCS, an asthma-related emergency room [ER] visit, or hospitalisation); prior asthma medication use; OCS use; and blood eosinophil count and serum IgE recorded pre-treatment for patients currently treated with omalizumab.

At the study visit, patient demographics, medical history, asthma disease history, therapy history, and asthma-related healthcare utilisation history were documented. Patient-reported outcomes included: Asthma Control Questionnaire (ACQ-5), St. George's Respiratory Questionnaire (SGRQ) and the standardised Asthma Quality of Life Questionnaire (AQLQ[S]).

Clinical assessments included a physical examination, spirometry and assessment of reversibility if not available

Table 1. Eligibility criteria for each of the biologics.

Criteria	Therapy				
	Mepolizumab	Omalizumab			Reslizumab
		AUS/CAN/USA ^a	EU1	EU2 ^e	
Asthma exacerbations requiring OCS, ER or hospitalisation, in the previous 12 months	≥2	≥1 ^b	≥1 ^b	≥2 ^b	≥1
Eosinophil count	≥150 cells/μL at study visit or ≥300 cells/μL in the previous 12 months	N/A	N/A	N/A	≥400 cells/μL at screening or study visit
Baseline IgE	N/A	IgE levels and weight as per AUS/CAN/USA labels ^c	IgE levels and weight as per EU label ^c	IgE levels and weight as per EU label ^c	N/A
Allergic asthma	N/A	RAST positive ^d	RAST positive	RAST positive	N/A
Lung function	N/A	N/A	≤80% FEV ₁	≤80% FEV ₁	≥12% airway reversibility to SABA administration
ACQ-5 score	N/A	N/A	N/A	≥1.5	≥1.5

Notes. ^aAUS/CAN/USA, Australian, Canadian, United States eligibility criteria. ^bThe AUS/CAN/USA omalizumab labels did not specify any requirement for exacerbations requiring OCS, ER or hospitalisation and the EU label gave no defined time period or specific number of 'multiple documented severe asthma exacerbations' that had to have been experienced. ^cDosing tables are available in the prescribing information for each country. ^dPatient had a positive skin test or *in vitro* testing (i.e., a blood test for allergen-specific IgE antibodies such as the RAST) for one or more perennial aeroallergens (e.g., house dust mite *Dermatophagoides farinae*, *D. pteronyssinus*) and animal dander (dog, cat). ^eThis was a proxy for the EU label for omalizumab, which states that patients should have experienced 'multiple documented severe asthma exacerbations' and 'frequent daytime symptoms or nighttime awakenings'. ACQ-5, Asthma Control Questionnaire; ER, emergency room; EU, European Union; IgE, immunoglobulin E; FEV₁, forced expiratory volume in 1 second; N/A, not applicable; OCS, oral corticosteroid; RAST, radioallergosorbent test; SABA, short-acting β_2 -agonist.

from medical records. Measurement of pulmonary function was obtained using spirometry equipment according to ATS recommendations [13]. For FEV₁ and FVC, the largest values from three acceptable efforts (maximum of eight attempts) were recorded, even if they did not come from the same effort. For the reversibility assessment, the patient was administered four puffs of an SABA and a second spirometry assessment was performed within 10–15 minutes.

Laboratory assessments included a blood sample for haematology evaluations, blood eosinophil counts, total serum IgE, and specific IgE (radioallergosorbent test).

Routine safety assessments were incorporated into study visits, and included reporting of adverse events (AEs) and serious AEs (SAEs). Any study-related or GSK product-related event as assessed by the investigator was reported. Vital signs (pulse rate and blood pressure) were also measured at the study visit.

Study endpoints: Eligibility

The primary endpoint was the percentage of patients with severe asthma eligible for ≥1 biologic treatment, including mepolizumab, omalizumab and reslizumab. Eligibility for mepolizumab and reslizumab, not approved for marketing at the time of the study, was determined by clinical trial inclusion criteria from key Phase III trials

[14, 15]. Eligibility for omalizumab was determined by regulatory labels (Australia [AUS], Canada [CAN], the European Union [EU] and the United States of America [USA]), as this varies between regions (Supplementary Table S1).

Patients currently treated with omalizumab were automatically considered eligible for omalizumab without evaluating eligibility criteria, as it was expected that omalizumab treatment would have affected the baseline characteristics (e.g., IgE levels) thus altering the patient's ability to meet the eligibility criteria for omalizumab.

Eligibility for the three treatments is summarised in Table 1. The requirement for omalizumab eligibility across all countries as having had ≥1 prior exacerbation requiring OCS, ER or hospitalisation in the past 12 months was set as a marker of inadequately controlled asthma based on the joint ERS/ATS guidelines. In addition, two sets of eligibility criteria were used for the EU due to ambiguity in the labelling. EU1 was protocol defined, and EU2 was a sensitivity analysis, based on external expert advice, which tightened the eligibility criteria by increasing the required exacerbation frequency from ≥1 to ≥2 and adding an ACQ-5 score ≥1.5. There was no equivalent requirement for multiple exacerbations in AUS, CAN and US product labels, but patients had to be 'inadequately controlled'; thus, ≥1 exacerbation was viewed as an acceptable eligibility criterion for omalizumab in non-EU patients. An analysis of treatment

eligibility for omalizumab by the AUS, CAN and US labels produced an identical eligible patient cohort, therefore the results for these three countries are presented as a single cohort. Eligibility for mepolizumab and reslizumab differed by required exacerbation frequency (≥ 2 and ≥ 1 , respectively), eosinophil count (≥ 150 and ≥ 400 cells/ μL at study visit, respectively) and lung function (no requirement for mepolizumab eligibility and $\geq 12\%$ airway reversibility to SABA administration required for reslizumab eligibility).

Statistical analyses

Sample size

A sample size calculation was performed to determine the number of patients needed in the study to allow for meaningful and interpretable estimates of eligibility and overlap. This was achieved by calculating the number of subjects required for exact confidence limits to be within approximately 7% of the point estimate of eligibility. For the proportion of patients with severe asthma eligible for mepolizumab and omalizumab (including those currently using omalizumab), a sample size of 750 patients ensured the 95% exact confidence interval (CI) for this proportion would lie within $\pm 6.7\%$ of any estimated proportion.

Study populations

Treatment eligibility was estimated in two study populations: (1) total cohort, comprising all patients who had sufficient information to assess eligibility for all treatments; and (2) sub-cohort, patients not currently treated with omalizumab.

As the a priori intent of the study was to describe the proportion of patients with severe asthma who were eligible for treatment with a biologic, the main data presentation will focus on those patients not currently treated with omalizumab (sub-cohort), which represents patients in clinical practice who would be eligible for new treatment initiation with any available biologic. The total cohort, reflecting patients with severe asthma from an epidemiological perspective, including those already treated with omalizumab, is also presented for reference.

Data analyses

Eligibility estimates were the proportion of patients eligible for a given treatment, in the case of overlaps, among patients eligible for another treatment. The 95% CI for this binomial proportion was calculated using the Clopper–Pearson method [16]. Calculations were performed in SAS 9.2 (SAS Institute, Cary, NC).

Results

Patients

Of 791 patients screened, 748 had severe asthma as defined in the protocol. Of these, 670 could be assessed for eligibility for all three treatments and were included in the total cohort. In the total cohort, 502 patients were not currently treated with omalizumab and were included in the sub-cohort (Figure 1). Overall, demographic and patient characteristics were comparable between the two cohorts (Table 2). The majority of patients had uncontrolled asthma according to the assessment of their symptom control, maintenance OCS use, and exacerbation history. Only 8–9% of patients in the total cohort and sub-cohort had controlled asthma (no clinically significant asthma exacerbations in the past 12 months, no current OCS maintenance use, and an ACQ-5 score of < 0.75). An additional 8% were considered partly controlled, fulfilling the same criteria as above but with an ACQ-5 score of ≥ 0.75 to < 1.5 .

Eligibility and overlap

Eligibility for one biologic therapy

In the total cohort ($N = 670$), 137 (20.4%) were eligible for mepolizumab and 34 (5.1%) were eligible for

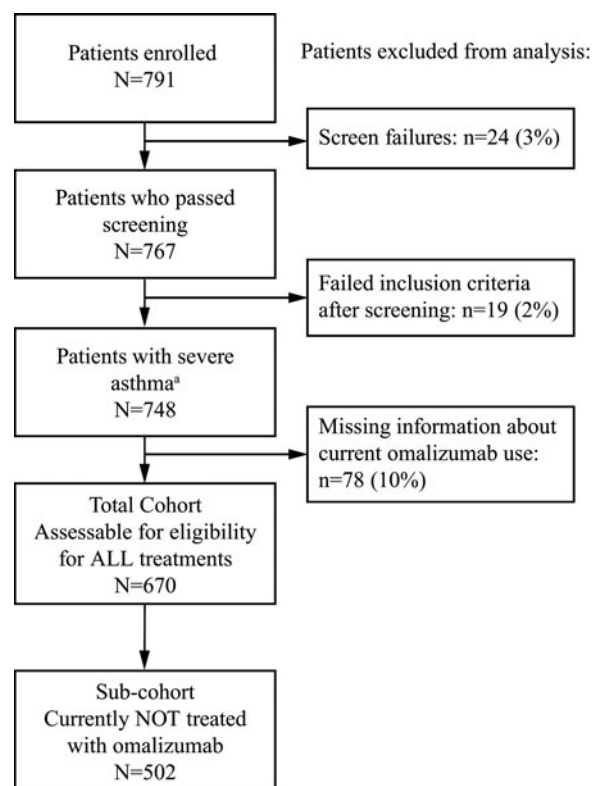


Figure 1. Study flow diagram showing study populations. ^aAs defined by the protocol.

Table 2. Demographics and baseline characteristics (all patients and those not currently treated with omalizumab [sub-cohort]).

Demographic characteristics	Total cohort (N = 670)	Sub-cohort (n = 502)
Age, years, mean (range)	51 (12–89)	51 (12–89)
Sex, female, n (%)	415 (62)	309 (62)
Duration of asthma, years, mean (SD)	26 (17)	26 (17)
Current OCS use, n (%)	94 (14)	66 (13)
Clinically significant exacerbations in the previous 12 months, mean (SD) ^a	1.2 (1.6)	1.2 (1.5)
Lung function, pre-bronchodilator		
% predicted FEV ₁ , mean (SD)	69 (21)	68 (21)
FEV ₁ : FVC, mean (SD)	0.68 (0.13)	0.68 (0.13)
% airway reversibility FEV ₁ , mean (SD)	13 (16)	13 (16)
Airway reversibility ≥12%, n (%)	268 (40)	205 (41)
Patient-reported outcomes, mean (SD)		
SGRQ total score	42.2 (20.0)	42.4 (20.0)
ACQ-5 score	2.08 (1.26)	2.09 (1.23)
AQLQ[S] total score	4.6 (1.3)	4.6 (1.3)
ASUI score	0.68 (0.24)	0.68 (0.23)
Blood eosinophil counts		
Geometric mean (GSD), cells/μL	186 (1001)	187 (1001)
≥150 cells/μL, n (%)	425 (63)	317 (63)
≥400 cells/μL, n (%)	139 (21)	104 (21)
Total IgE, KU/L, geometric mean (SD log)	155 (1.59)	109 (1.56)

Notes. ^aClinically significant exacerbations defined as those requiring OCS and/or ER visit and/or hospitalisation; ACQ-5, Asthma Control Questionnaire; ASUI, Asthma Symptom Utility Index; AQLQ[S], standardised Asthma Quality of Life Questionnaire; ER, emergency room; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; GSD, geometric standard deviation; IgE, immunoglobulin E; OCS, oral corticosteroids; SD, standard deviation; SGRQ, St. George's Respiratory Questionnaire.

reslizumab. Eligibility for omalizumab varied depending on the eligibility criteria used (AUS/CAN/USA: 41.0%; EU1: 38.4%, EU2: 30.6%). Broadly comparable results for mepolizumab and reslizumab eligibility were shown for the sub-cohort (Table 3). Omalizumab eligibility according to any of the three criteria used was lower (between 7.4 and 21.3%) in patients not currently treated with omalizumab (sub-cohort) than in the total cohort (Table 3).

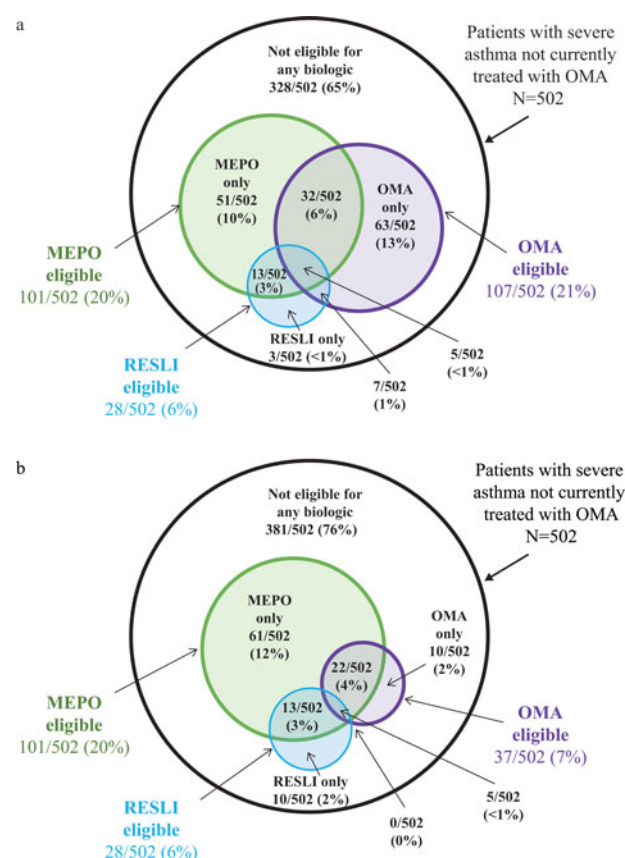
Eligibility for multiple biologic therapies

Treatment eligibility and overlap for patients not currently treated with omalizumab is summarised in Table 4

Table 3. Eligibility for treatment with biologics among patients with severe asthma (all patients and those not currently treated with omalizumab [sub-cohort]).

		Total cohort (N = 670)		Sub-cohort (n = 502)
Eligible for	n	% (95% CI)	n	% (95% CI)
Mepolizumab	137	20.4 (17.5, 23.7)	101	20.1 (16.7, 23.9)
Omalizumab				
AUS/CAN/USA	275	41.0 (37.3, 44.9)	107	21.3 (17.8, 25.2)
EU1	257	38.4 (32.7, 42.2)	89	17.7 (14.5, 21.4)
EU2	205	30.6 (27.1, 34.2)	37	7.4 (5.2, 10.0)
Reslizumab	34	5.1 (3.5, 7.0)	28	5.6 (3.7, 8.0)

Notes. AUS, Australia; CAN, Canada; CI, confidence interval; EU, European Union; USA, United States of America.

**Figure 2.** Eligibility for treatment with biologics among patients with severe asthma not currently treated with omalizumab based on A) AUS/CAN/USA and B) EU2 omalizumab eligibility criteria. AUS, Australia; CAN, Canada; MEPO, mepolizumab; OMA, omalizumab; RESLI, reslizumab; USA, United States of America.

and Figure 2. About one-third of patients eligible for mepolizumab were also eligible for omalizumab (AUS/CAN/USA: 37%; EU1: 37%; EU2: 27%). In contrast, among patients eligible for omalizumab, eligibility for mepolizumab varied considerably depending on the eligibility criteria used (AUS/CAN/USA: 35%; EU1: 42%, EU2: 73%). Eligibility for reslizumab was relatively low in patients eligible for mepolizumab (18%) or omalizumab (AUS/CAN/USA: 11%; EU1: 14%; EU2: 14%). However, between 65% and 76% of patients were not eligible for treatment with any biologic therapy, depending on the omalizumab eligibility criteria used (AUS/CAN/USA or EU2; Figure 2).

Broadly comparable results were observed in the total cohort (Supplementary Table S2).

Description of asthma population by treatment eligibility

Overall, among patients not currently treated with omalizumab (sub-cohort), those eligible for each of

Table 4. Summary of treatment eligibility (patients not currently treated with omalizumab [sub-cohort]).

Also eligible for	Eligibility <i>n</i> (%) [95% CI]				
	Mepolizumab <i>n</i> = 101	Omalizumab			Reslizumab <i>n</i> = 28
		AUS/CAN/USA <i>n</i> = 107	EU1 <i>n</i> = 89	EU2 <i>n</i> = 37	
Mepolizumab	—	37 (34.6) [25.6, 44.4]	37 (41.6) [31.2, 52.5]	27 (73.0) [55.9, 86.2]	18 (64.3) [44.1, 81.4]
Omalizumab (EU1)	37 (36.6) [27.3, 46.8]	—	—	—	12 (42.9) [24.5, 62.8]
Omalizumab (EU2)	27 (26.7) [18.4, 36.5]	—	—	—	5 (17.9) [6.1, 36.9]
Omalizumab (AUS/CAN/USA)	37 (36.6) [27.3, 46.8]	—	—	—	12 (42.9) [24.5, 62.8]
Reslizumab	18 (17.8) [10.9, 26.7]	12 (11.2) [5.9, 18.8]	12 (13.5) [7.2, 22.4]	5 (13.5) [4.5, 28.8]	—

Notes. AUS, Australia; CAN, Canada; CI, confidence interval; EU, European Union; USA, United States of America.

the three biologic treatments had similar demographics (Table 5). Mepolizumab-eligible patients had more frequent OCS maintenance use than omalizumab- and reslizumab-eligible patients. Omalizumab-eligible patients had a longer duration of asthma compared with mepolizumab- and reslizumab-eligible patients. Mepolizumab-, reslizumab- and omalizumab (EU2)-eligible patients had a higher exacerbation rate, worse HRQoL (measured by SGRQ), and worse asthma control (measured by ACQ-5), compared with the other two omalizumab-eligible patient groups (AUS/CAN/USA and EU1), suggesting more severe disease in these three groups, as indicated by the eligibility criteria. However, all patient eligibility groups had poor asthma control, as indicated by mean ACQ-5 score of >2. As a result of the eligibility criteria, mean blood eosinophil counts were higher in mepolizumab-eligible and reslizumab-eligible patients, compared with omalizumab-eligible patients.

Similar to the sub-cohort, in the total cohort, omalizumab-eligible patients (AUS/CAN/USA, EU1 and EU2) had a lower exacerbation rate, better HRQoL (assessed by SGRQ), lower mean blood eosinophil counts and slightly better asthma control (assessed by ACQ-5) than mepolizumab- and reslizumab-eligible patients (Supplementary Table S3).

Safety

During this cross-sectional study, eight patients reported AEs assessed as study related by the investigator; there were no reports of SAEs, deaths or AEs that led to withdrawal. No treatments were administered except for SABA as part of the reversibility test.

Discussion

Severe asthma is a heterogeneous disease consisting of several different phenotypes [6]. These phenotypes can

Table 5. Demographic and baseline characteristics by treatment eligibility (patients not currently treated with omalizumab [sub-cohort]).

Demographic characteristic	Mepolizumab-eligible <i>n</i> = 101	Omalizumab-eligible			Reslizumab eligible (<i>n</i> = 28)
		AUS/CAN/USA (<i>n</i> = 107)	EU1 (<i>n</i> = 89)	EU2 (<i>n</i> = 37)	
Age, years, mean (range)	48 (15–77)	45 (14–77)	48 (15–77)	44 (15–69)	44 (13–75)
Gender, female, <i>n</i> (%)	66 (65)	70 (65)	53 (60)	25 (68)	19 (68)
Duration of asthma, years, mean (SD)	24 (16)	29 (18)	30 (17)	28 (15)	20 (14)
Current OCS use, <i>n</i> (%)	19 (19)	13 (12)	12 (13)	7 (19)	4 (14)
Clinically significant exacerbations in the previous 12 months, mean (SD) ^a	3.2 (1.5)	1.9 (1.2)	2.1 (1.4)	2.9 (1.3)	2.8 (2.3)
Lung function, pre-bronchodilator					
% predicted FEV ₁ , mean (SD)	64 (20)	71 (20)	61 (13)	59 (14)	56 (15)
FEV ₁ /FVC ratio, mean (SD)	0.66 (0.13)	0.70 (0.12)	0.66 (0.10)	0.67 (0.10)	0.61 (0.13)
% airway reversibility FEV ₁ , mean (SD)	14 (13)	14 (24)	17 (25)	25 (35)	24 (10)
Airway reversibility ≥12%, <i>n</i> (%)	50 (50)	45 (42)	46 (52)	23 (62)	28 (100)
Patient-reported outcomes, mean (SD)					
SGRQ total score	53.2 (18.5)	45.1 (20.0)	49.3 (18.8)	57.5 (15.5)	56.8 (17.0)
ACQ-5 score	2.64 (1.42)	2.19 (1.31)	2.44 (1.33)	3.25 (1.09)	3.11 (1.04)
AQLQ[S] total score	4.1 (1.24)	4.4 (1.22)	4.2 (1.23)	3.5 (0.96)	3.9 (1.10)
ASUI score	0.55 (0.25)	0.65 (0.23)	0.60 (0.24)	0.50 (0.22)	0.50 (0.22)
Blood eosinophil counts					
Geometric mean (SD log), cells/μL	301 (0.78)	197 (0.96)	241 (0.92)	207 (1.08)	611 (0.40)
≥150 cells/μL, <i>n</i> (%)	94 (93)	71 (66)	64 (72)	25 (68)	28 (100)
≥400 cells/μL, <i>n</i> (%)	33 (33)	24 (22)	26 (29)	9 (24)	28 (100)
Total IgE, KU/L, geometric mean (SD log)	135 (1.61)	140 (0.78)	175 (0.89)	172 (0.82)	173 (1.47)

Notes. ^aClinically significant exacerbations defined as those requiring OCS and/or ER visit and/or hospitalisation; ACQ, Asthma Control Questionnaire; AQLQ[S], standardised Asthma Quality of Life Questionnaire; ASUI, Asthma Symptom Utility Index; AUS, Australia; CAN, Canada; ER, emergency room; EU, European Union; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; OCS, oral corticosteroids; SD, standard deviation; SGRQ, St. George's Respiratory Questionnaire; USA, United States of America.

involve multiple underlying pathobiologic mechanisms, or endotypes, involving specific inflammatory pathways (e.g., IgE and IL-5), which can be the target of different biologic treatments [6, 17]. There is a lack of data describing the proportion of patients with severe asthma, who were eligible for biologic therapies targeting IgE and/or IL-5, and the characteristics of the respective overlap population.

The IDEAL study is the first prospective, observational study to identify and describe the population of patients with severe asthma eligible for mepolizumab, omalizumab or reslizumab across multiple countries, according to a standardised set of criteria. Eligibility for each biologic was based on labelling or protocol-defined inclusion criteria. Consequently, exacerbation history was a key requirement that differed between the three treatments. Notably, none of the approved omalizumab labels actually require patients to have experienced a specific number of clinically significant exacerbations over a defined time period, but it was set as a marker of inadequately controlled asthma based on the joint ERS/ATS guidelines [2]. Also, patients already treated with omalizumab were included in the omalizumab-eligible population irrespective of exacerbation frequency. Therefore, while the inclusion of current omalizumab users (total cohort) gives a reflection of patients with severe asthma from an epidemiology perspective, this does not reflect eligibility for mepolizumab and reslizumab treatment initiation from a practical perspective in the clinical setting. Additionally, treatment with omalizumab may have impacted clinical and biological criteria for eligibility, such as exacerbation frequency, ACQ-5 score, OCS use or eosinophil counts. To address this issue we analysed data in a sub-cohort of patients not currently receiving omalizumab. Overall, we found that mepolizumab and reslizumab eligibility and disease burden were broadly comparable between the cohorts.

Of the patients not currently taking omalizumab (sub-cohort), representing potential new users of biologic treatment in clinical practice, 20% were eligible for mepolizumab, compared with 7–21% eligible for omalizumab, depending on the eligibility criteria used. Interestingly, in the total cohort including patients currently on omalizumab, a similar proportion of patients were eligible for mepolizumab (20%), suggesting that omalizumab treatment may not have had a large impact on meeting the eligibility criteria used for mepolizumab. Omalizumab eligibility was higher in the total cohort (31–41%) than in the sub-cohort, reflecting the inclusion of those patients already on omalizumab independent of their current clinical status [8].

A small proportion of patients with severe asthma (6%) were found to be eligible for treatment with reslizumab

according to the protocol-defined criteria from the published reslizumab Phase III study [14]. However, as per protocol and in line with ATS/ERS guidelines, all patients with severe asthma in the IDEAL study must have been treated with high-dose ICS and another controller, which was not a criterion used in the clinical trials for reslizumab; the reslizumab trials also included patients on medium-dose ICS. This population restriction possibly contributed to the low eligibility observed for reslizumab in patients with severe asthma on high-dose ICS and another controller.

We anticipated there would be an overlap in the proportion of patients eligible for anti-IL-5 therapy and anti-IgE therapy based on the possibility of an overlap in the underlying asthma endotypes. In the current study, we found that in patients who were not currently taking omalizumab, the overlap from the perspective of mepolizumab eligibility was relatively limited, with about one-third of patients (27–37%) also eligible for omalizumab depending on the eligibility criteria used. Interestingly, the overlap between mepolizumab and reslizumab was even lower (18%) despite both drugs being monoclonal anti-IL-5 antibodies. This was largely driven by the different thresholds of eosinophils applied in the eligibility criteria, with the 400 cells/ μ L criterion for reslizumab being the limiting factor with the greatest impact on eligibility.

Among the omalizumab-eligible patients in the sub-cohort, the overlap with mepolizumab eligibility showed a high degree of variability (35% vs 73% for AUS/CAN/USA and EU2 criteria, respectively). This variability was largely attributable to differences in the various country labels. For example, the high degree of overlap (73%) between patients eligible for omalizumab (EU2) and mepolizumab was driven by the requirement for a similar exacerbation history. In contrast, the overlap between omalizumab and reslizumab was consistently low (11–14%) across the different omalizumab eligibility criteria groups; this was mostly driven by the 400 cells/ μ L criteria for reslizumab.

Across both cohorts, the number of patients eligible for reslizumab was the lowest of the three biologics evaluated. Among reslizumab-eligible patients not currently treated with omalizumab, the overlap in treatment eligibility with two other biologics was variable. Interestingly, the lower range of the overlap (18%) in eligibility for reslizumab and omalizumab (EU2) was mostly driven by the differences in exacerbation history criteria. The larger overlap with mepolizumab eligibility in reslizumab-eligible patients (64%) was expected, as both drugs are anti-IL-5 monoclonal antibodies. Additionally, the eosinophil criterion for reslizumab was a subset of the mepolizumab criteria; however, due to the differences in

exacerbation history criteria applied, the overlap was not 100%.

Previous studies have shown that in a general asthma population, the overlap of patients with eosinophilic asthma and allergic asthma was 68% using the eosinophil count cut-off of 150 cells/ μ L [18]. In the current study, there was a 27–73% overlap in mepolizumab and omalizumab eligibility (i.e., eosinophilic and allergic asthma, respectively), in patients not currently treated with omalizumab.

In the current study, we found that a considerable proportion of patients (65–76%) were not eligible for any of the three treatments evaluated. This was mainly due to patients not fulfilling criteria for having ≥ 1 or ≥ 2 exacerbations requiring OCS, ER or hospitalisation in the past 12 months. This highlights the clear remaining unmet medical need in this severe asthma cohort, largely being uncontrolled or only partially controlled.

A limitation of this study was that Phase III trial criteria were used to define eligibility for mepolizumab and reslizumab, rather than the current labels. Eligibility for mepolizumab based on the Phase III trials differs from the EU license in terms of patient age (≥ 12 vs ≥ 18 years, respectively), although it is consistent with the US license [10, 11, 15]. Similarly, Phase III reslizumab trial criteria differ from both the US and EU licenses in terms of patients age (≥ 12 vs ≥ 18 years) [12, 14, 23]. Ultimately, however, regulatory labels and treatment guidelines will define eligibility for these biologics, which may vary between regions. It is also possible that recruitment sites and countries could have led to bias that potentially impacted results. Additionally, there is an unknown selection bias for patients who volunteer for this type of study.

Strengths of this study include the potential to collect data during a single study visit on the same day as screening, eliminating the opportunity for attrition of the study population through withdrawal or loss to follow-up. The prospective nature of patient recruitment addressed the challenges encountered with retrospective database analyses with regard to medicine eligibility for patients with existing severe asthma (e.g., caused by incomplete ascertainment or limited availability of data required for the determination of product eligibility) and also provided the opportunity to collect patient-reported data to more precisely measure the impact of severe asthma on patients.

Conclusions

In conclusion, as previous studies have shown that mepolizumab, omalizumab and reslizumab are efficacious at reducing exacerbation rates in their respective

patient populations [14, 15, 19–22], an understanding of the proportion of the severe asthma population eligible for each treatment could aid clinical decision-making. This study highlights that patient groups eligible for treatment with anti-IL-5 or anti-IgE therapies are often distinct, emphasising the different phenotypes and endotypes in severe asthma. It is important to recognise that among the severe asthma population enrolled, only a small proportion was actually controlled. The IDEAL study also highlights the limited treatment options for patients with severe asthma, since a considerable proportion of uncontrolled patients were not eligible for any of the biologics. Although there was overlap in treatment eligibility among patients with different phenotypes of severe asthma, it varied depending on the population evaluated; with experience, the utility of one biologic over the other in the overlap population will emerge.

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Declaration of interest

FCA, HM, NBG, J-YS, LMN, ESB and SMC are GlaxoSmithKline (GSK) employees. FCA, HM, NBG, LMN, ESB, RYS and SMC are GSK shareholders. RYS was an employee of GSK at the time of the study and is now employed by UCB BioSciences.

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