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Early View

Original research article

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Characteristics of severe asthma patients on biologics; a real-life European registry study

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Key words: *severe asthma, biological agents, asthma clinical trials.*

Take Home message

The European severe asthma population that starts anti-IL5(R) is broader than the one represented in randomized controlled trials (RCTs). Centralize clinical real-life registries is an important way to align the management and the assessment of the disease. This study will be an important start for future prospective study to assess the effectiveness of biologics in real-life.

Abstract

Background

The use of anti-IL5 for severe asthma is based on criteria from randomized controlled trials(RCTs) but in real-life patient might not fulfil eligibility criteria but benefit from biologics. We aimed to: characterise patients starting in anti-IL5(R) in Europe and evaluate the discrepancies between initiation of anti-IL5(R) in real-life and in RCTs.

Material and methods

We performed a cross-sectional analysis with data from the severe asthma patients at the start of anti-IL5(R) in the Severe Heterogeneous Asthma Research collaboration Patient-centered(SHARP-Central)registry. We compared the baseline characteristics of the anti-IL5(R) from 11 European countries within SHARP with the baseline characteristics of the severe asthma patients from 10 RCTs (4 for mepolizumab, 3 for benralizumab and 3 for reslizumab). Patients were evaluated following eligibility criteria from the RCTs of anti-IL5 therapies.

Results

Patients anti-IL5(R) starters in Europe (n=1231) differed in terms of smoking history, clinical characteristics and medication use. The characteristics of severe asthma patients in SHARP Registry differed from the characteristics of patients in RCTs. Only 327(26,56%) fulfilled eligibility criteria of all the RCTs; 24 patients were eligible for mepolizumab,100 for benralizumab and 52 reslizumab. The main characteristics of ineligibility were: pack/years ≥ 10, respiratory diseases other than asthma, ACQ score ≤ 1.5, low dose ICS.

Conclusion

A large proportion of patients in the SHARP registry would not have been eligible for anti-IL-5(R) treatment RCTs, demonstrating the importance of real life cohorts in describing the efficacy of biologics in a broader population of patients with severe asthma.

Abbreviations:

IL: Interleukin

RCTs: Randomized Controlled Trials

SHARP: Severe Heterogeneous Asthma Research collaboration Patient-centered

ACQ: Asthma Control Questionnaire

ICS: Inhaled corticosteroids

ERS/ATS: European Respiratory Society/American Thoracic Society

RAPSODI: Registry of Adult Patients with Severe asthma for Optimal DIsease management

CRC: Clinical research Collaboration

FDR: false discovery rate

IgE: Immunoglobulin E

MCAR: Missed Completely at Random

HR: Croatia

HU: Hungary

LT: Lithuania

LV: Latvia

NL: Netherlands

PL: Poland

RO: Romania

RS: Serbia

SE: Sweden

SI: Slovenia

TR: Turkey

BMI: Body Mass Index

FEV1: Forced Expiratory Volume in the 1st second

FVC: forced vital capacity

FeNO: Fraction exhaled nitric oxide

OCS: oral corticosteroids

LABA: Long-acting beta-agonists

LAMA: Long-acting muscarinic antagonists

LTRA: Leukotriene receptor antagonists

OSAS: Obstructive sleep apnoea syndrome

EGPA: Eosinophilic granulomatosis with polyangitis

ABPA: Allergic bronchopulmonary aspergillosis

Introduction

Asthma is a common chronic disease affecting approximately 5% to 10% of the global population, with an estimated 3%–10% of asthma patients suffering from the severe form of the disease[1]. Since the introduction of novel biologics for severe asthma, significant progress has been made in the management of this debilitating condition, starting with the anti-IgE monoclonal antibody omalizumab and more recently, with the anti-interleukin (IL)-5/IL-5R antibodies (mepolizumab, reslizumab and benralizumab) [2]. The use of biologics is typically restricted to patients who fulfil the definition of severe asthma according to European Respiratory Society (ERS) /American Thoracic Society (ATS) guidelines which are based on evidence of clinical efficacy from randomized controlled trials (RCTs) conducted for regulatory purposes [3].

In clinical practice, however, it has been demonstrated that only 25% to 35% of severe asthma patients who use biologicals meet inclusion criteria from RCTs [4]. While the reasons for this heterogeneity across Europe, and indeed more widely, are unknown, it is plausible that they are due to variability in climate, healthcare systems and expertise. Whether, and to what extent, this influences the decisions about the treatment of severe asthma is also unknown. A study using the Dutch national RAPSODI Registry (Registry of Adult Patients with Severe asthma for Optimal DIsease management)[5], has shown that many patients with severe asthma do not meet the strict ERS/ATS eligibility criteria, but still benefit in a real-life setting from mepolizumab therapy [6]. Moreover, a recent analysis of clinical data from several European national registries, conducted by our Clinical research Collaboration (CRC) called SHARP (Severe Heterogeneous Asthma Research collaboration, Patient-centred) has shown notable heterogeneity of clinical characteristics amongst severe asthma patients [7]. SHARP CENTRAL Registry has been developed with the purpose to collect real-world data on diagnosis and treatment of severe asthma patients.

The criteria for the prescription of biologicals for severe asthma set by the European Medicine Agency (EMA) are also very broad. Roughly, the anti-interleukin (IL)-5/IL-5R biologics are indicated as “add-on therapies for adult patients with severe eosinophilic asthma inadequately controlled despite regular asthma treatment.” Therefore, the prescription criteria of these medications are highly variable in Europe[8]. Hence, it is interesting to investigate whether and to what extent European countries differ in the type of patients to whom anti IL-5 biologicals are prescribed in real life, and whether the characteristics of these patients differ from those in the phase III RCTs. This will probably depend largely on differences in local guidelines, in organization of the health care system and in access to expensive medicines.

The overall objective of the current study was to assess to what extent European countries differ in their application of the standard eligibility criteria of RCTs for initiating use of biologics in severe asthma patients. The specific aims of the study were

to: 1) characterise patients starting biologic treatment in Europe; 2) compare their characteristics with those from the severe asthma populations participating in RCTs and 3) evaluate the potential discrepancies between initiation of anti-IL-5(R) in real life and in RCTs as judged by different inclusion and exclusion criteria.
We hypothesized that characteristics of patients who are about to start using biologics differ between European countries, and do not always match the eligibility criteria specified in clinical trials. If the population prescribed anti-IL-5 biologics in real life is broader than the population represented in clinical trials, this could imply that a greater number of patients might benefit from these targeted therapies.
For this study, we used data collected in the SHARP CENTRAL Registry, a centralised registry hosted in the Netherlands, containing data from 11 European countries developed for the purpose of providing fully harmonised and longitudinal real-world data from people with severe asthma.

Materials and Methods

Study design and subjects

We conducted a cross-sectional multicenter, observational registry-based study, which analysed patient clinical characteristics before starting one of the approved anti-IL-5 biologicals (mepolizumab, benralizumab and reslizumab). Data were collected in the SHARP CENTRAL registry, taking into account the characteristics of patients before starting with one of the biologicals and were stratified by country. Remedial factors to evaluate asthma such as mistakes in inhaler technique, poor adherence, unmitigated allergen exposure, and inadequate management of comorbidities should have been prior considered, to differentiate severe to difficult to treat asthma as stated in the national guidelines [1]. All patients have signed an informed consent for their data to be used for research. The study was exempted from approval by ethics committees because it only used data from medical records.

Data Source

Data were retrieved from the medical patients' records from different hospitals in each country on an annual basis and captured in an electronic case report forms platform (CASTOR Electronic Data Capture (EDC)[9]) in a standardized way. We included clinical, biological and functional information of severe asthma patients before the start of an anti-IL5(R) treatment. Data on number of exacerbations were retrieved for the analysis and exacerbation was defined as: worsening of respiratory symptoms that required OCS course of minimal 3 days or doubling the normal oral dose in the previous 12 months. The SHARP CENTRAL registry database included patients initiating one of the three anti-IL5(R) biologics between 01/01/2016 and 24/09/2021.

Comparison of eligibility criteria for biologic treatment between the SHARP-Central registry and RCTs

The characteristics of patients from phase III RCTs of anti-IL5(R) were compared with those of patients starting treatment in SHARP Central. In parallel, a literature review of the phase III RCTs conducted before the approval of anti-IL5 biologics was performed, focusing on the selection of the inclusion/exclusion criteria to assess eligibility and ineligibility [10–19] (**figure S1** in the Supplementary Material). According to the study of Richards et al. [6], we defined trial ineligibility as: fulfilling at least one of the exclusion criteria stated in the selected RCTs; or not fulfilling one of more of the inclusion criteria stated in RCTs of the patient prescribed one of the biologicals.

Analysis

For the first aim, a descriptive analysis was performed to evaluate the patient clinical characteristics in different countries. Data were stratified per country and summarized using proportions, means and standard deviations.
For the second aim, data from the SHARP registry was compared with data derived from RCTs using Welch-modified t-test for continuous and $\chi 2$ tests for categorical variables. A false discovery rate (FDR) correction of 10% was applied to reduce the risk of false positives due to the multiple comparisons. FDR-corrected P values <0.05 were considered as significant differences. If the publications of the selected RCTs and the clinical reports only reported the mean and distribution of the individual treatment arms (mepolizumab, benralizumab or reslizumab), the aggregated averages and distribution were calculated.
For the third aim, a selection of trials' eligibility and ineligibility was made and patients from the registry were evaluated according to the eligibility criteria previously defined. In this way, we distinguished within SHARP Central patients eligible and not eligible for RCTs, according to the fulfilment of the eligibility criteria. This analysis was used to determine the number of eligible patients included in SHARP Central and to evaluate the characteristics of not eligible patients.
Missing data were considered Missed Completely at Random (MCAR) and, when necessary, a complete case analysis was performed to handle missing variables.
Statistical analysis was performed using R version 3.4.4.

Results

We analyzed data from SHARP CENTRAL Registry of 1231 severe asthma patients that initiated anti-IL-5 treatments such as benralizumab, mepolizumab or reslizumab. For the analysis, 11 countries were analyzed: Croatia (HR) with 106 asthma patients (n = 106), Hungary (HU) n = 48, Lithuania (LT) n= 60, Latvia (LV) n=15, Netherlands (NL) n=814, Poland (PL) n=17, Romania (RO) n=21, Serbia (RS) n=45, Sweden (SE) n=20, Slovenia (SI) n=43 and Turkey (TR) n=42. Among them were 159 patients with severe asthma who had previously used another biologic for severe asthma (specifically Omalizumab, anti-IgE monoclonal antibody), while 1072 patients with severe asthma were first initiators of anti-IL-5(R) treatment without prior use of any other biologics.

Characteristics of severe asthma patients' in European countries included in SHARP Central registry

A summary of the characteristics of patients among different countries is presented in **table 1**, including demographics, clinical characteristics, laboratory tests (blood differential cell counts, total IgE), pulmonary function tests and medication use.

Table 1. General characteristics of severe asthma patients before the start of anti-IL-5(R) stratified per country.

	HR (n =106)	HU (n=48)	LT (n=60)	LV (n=15)	NL (n= 814)	PL (n=17)	RO (n=21)	RS (n=45)	SE (n=20)	SI (n=43)	TR (n=42)
Age (mean (SD))	57.86 (13.99)	53.83 (10.90)	57.90 (12.41)	63.73 (11.07)	56.71 (13.44)	60.00 (12.12)	51.33 (12.69)	54.36 (10.01)	57.85 (15.16)	58.43 (10.82)	48.60 (11.80)
Asthma age at diagnosis (mean (SD))	39.09 (16.79)	33.48 (17.11)	38.38 (17.22)	34.00 (16.28)	37.63 (25.58)	25.94 (48.46)	36.16 (15.89)	41.64 (13.98)	36.00 (19.67)	42.52 (16.36)	36.52 (12.42)
Gender Female (%)	71 (67.0)	36 (75.0)	32 (53.3)	10 (66.7)	405 (49.8)	10 (58.8)	14 (66.7)	18 (40.0)	4 (20.0)	23 (53.5)	12 (28.6)
Smoking history (%)											
Never	68 (64.2)	39 (81.2)	41 (68.3)	10 (66.7)	436 (53.6)	13 (76.5)	14 (66.7)	32 (71.1)	10 (50.0)	28 (65.1)	31 (73.8)
Former	33 (31.1)	6 (12.5)	15 (25.0)	5 (33.3)	371 (45.6)	4 (23.5)	7 (33.3)	13 (28.9)	10 (50.0)	14 (32.6)	10 (23.8)
Active	5 (4.7)	3 (6.2)	4 (6.7)	0 (0.0)	7 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.4)
Pack/years (mean (SD))	22.52 (14.48)	12.78 (8.90)	13.61 (11.53)	18.60 (14.48)	15.21 (14.30)	27.50 (31.82)	20.43 (13.33)	25.00 (16.96)	8.75 (7.99)	20.68 (18.06)	6.60 (8.62)
BMI (mean (SD))	27.31 (5.62)	27.50 (5.06)	29.24 (5.01)	25.87 (5.37)	27.93 (5.50)	29.95 (4.75)	23.05 (3.67)	27.96 (6.62)	26.04 (5.20)	28.34 (5.72)	NaN (NA)
Compliance Yes (%)*	75 (70.7)	41 (85.4)	41(68.3)	15 (100)	183 (22.5)	0 (0.0)	20 (95.2)	43 (95.5)	20(100)	19 (44.2)	32 (76.2)
FEV1 prebd (l) (mean(SD))	1.71 (0.75)	1.56 (0.56)	1.97 (0.95)	1.43 (0.50)	2.37 (0.87)	1.89 (0.65)	1.78 (0.94)	1.92 (0.63)	2.44 (0.97)	2.23 (0.67)	2.11 (0.79)
FVC prebd (l) (mean(SD))	2.94 (1.12)	2.74 (0.92)	3.00 (1.04)	2.31 (0.90)	3.75 (1.14)	2.99 (1.03)	2.91 (0.88)	3.32 (1.09)	4.01 (1.34)	3.67 (1.01)	3.06 (1.12)
FEV1 prebd (%) (mean(SD))	64.86 (21.11)	55.64 (16.14)	67.53 (20.92)	55.56 (14.43)	76.01 (21.87)	67.65 (15.55)	60.64 (23.62)	67.14 (17.25)	74.54 (24.46)	79.59 (22.76)	78.09 (24.27)
FVC prebd (%) (mean(SD))	91.72 (22.22)	81.36 (20.39)	80.98 (16.97)	77.19 (18.10)	97.00 (18.40)	86.65 (16.12)	76.69 (23.15)	95.64 (20.63)	99.02 (20.97)	101.24 (18.32)	93.00 (18.63)
FEV1/FVC prebd (%) (mean(SD))	72.10 (14.08)	69.07 (12.23)	81.84 (15.36)	66.00 (13.36)	73.39 (27.32)	80.06 (16.69)	60.67 (15.87)	58.27 (9.93)	47.99 (50.34)	62.26 (12.91)	71.35 (14.42)
FEV1 postbd (l) (mean(SD))	1.74 (0.72)	1.65 (0.88)	1.77 (0.64)	1.57 (0.54)	2.52 (0.91)	2.21 (1.17)	NaN (NA)	1.98 (0.62)	1.95 (0.05)	1.59 (0.61)	1.92 (0.47)
FVC postbd (l)(mean(SD))	3.00 (0.98)	2.86 (1.00)	2.69 (0.83)	2.57 (0.95)	3.90 (1.17)	3.40 (1.29)	NaN (NA)	3.03 (0.73)	3.72 (0.36)	3.29 (0.45)	2.84 (0.61)
FEV1 postbd (%)(mean(SD))	62.76 (17.21)	56.00 (20.08)	63.67 (19.87)	62.40 (11.49)	80.95 (21.81)	71.00 (18.67)	NaN (NA)	71.39 (20.84)	59.97 (12.35)	67.33 (28.75)	71.25 (14.91)
FVC postbd (%) (mean(SD))	88.31 (17.55)	79.67 (16.64)	75.28 (14.38)	84.75 (19.40)	101.09 (17.78)	88.00 (13.32)	NaN (NA)	91.34 (18.35)	89.33 (13.61)	105.33 (2.31)	86.50 (12.21)
FEV1/FVC postbd (%) (mean(SD))	72.44 (14.86)	62.95 (16.66)	81.33 (16.01)	67.20 (14.82)	77.41 (22.33)	81.25 (8.66)	NaN (NA)	64.56 (10.70)	8.11 (93.58)	49.33 (21.36)	71.39 (18.17)
Blood neutrophils (cell/mcL)(mean(SD))	5.80 (7.90)	6.43 (7.48)	6.20 (11.74)	4.60 (1.47)	4.68 (10.23)	6.40 (3.19)	4.55 (1.26)	4.63 (1.97)	5.49 (2.51)	4.93 (2.75)	5.07 (1.41)
Blood eosinophils (cell/mcL)(mean(SD))	1106.63 (5771.10)	712.19 (400.28)	467.46 (631.09)	319.33 (336.21)	435.47 (468.65)	395.29 (257.17)	605.71 (1618.35)	405.87 (427.08)	358.45 (366.00)	366.43 (227.25)	353.34 (233.00)
IgE (mg/dl)	194.0	134.5	84.7	197.9	144.4	445.2	453.6(552.24)	136.8	160.0(552.55)	267.0(156.41)	187.0(323.40)

(mean(SD))	(449.34)	(768.90)	(206.68)	(2678.21)	(537.04)	(1059.14)		(238.93)			
FeNO (ppb) (mean(SD))	58.41 (47.35)	47.60 (21.70)	50.70 (37.11)	44.83 (46.15)	49.65 (40.26)	32.00 (NA)	NaN (NA)	66.00 (62.22)	55.79 (58.95)	76.88 (30.22)	15.40 (7.09)
OCS use (Yes) (%)	27 (25.5)	2 (4.2)	6 (10.0)	2 (13.3)	190 (23.3)	6 (35.3)	1 (4.8)	11 (24.4)	5 (25.0)	6 (14.0)	21 (50.0)
OCS (mg) (mean(SD))	4.65 (3.99)	2.41 (0.97)	5.01 (1.68)	3.86 (2.74)	10.22 (6.11)	5.11 (1.65)	4.15 (1.97)	3.74 (2.45)	3.62 (2.25)	2.99(1.35)	4.01 (1.37)
ACQ 5 (mean (SD))	1.29 (1.18)	1.27 (0.80)	2.08 (1.36)	1.73 (1.17)	2.20 (1.23)	1.47 (0.85)	2.17 (NA)	NaN (NA)	1.42 (0.59)	2.00 (NA)	1.33 (NA)
Exacerbations (%)§											
0-1 per year	26 (36.1)	2 (4.2)	14 (24.1)	2 (13.3)	253 (29.8)	1 (5.9)	4 (50.0)	15 (34.9)	10 (50.0)	23 (67.6)	31 (83.8)
2-5 per year	35 (48.6)	36 (75.0)	38 (65.5)	13 (86.7)	357 (43.8)	16 (94.1)	4 (50.0)	24 (55.8)	8 (40.0)	9 (26.5)	6 (16.2)
more than 5	11 (15.3)	10 (20.8)	6 (10.3)	0 (0.0)	117 (14.4)	0 (0.0)	0 (0.0)	4 (9.3)	2 (10.0)	2 (5.9)	0 (0.0)
ICS (mcg/day)(mean (SD))	375.75 (284.36)	535.65 (268.63)	798.40 (522.57)	360.20 (284.21)	902.30 (671.46)	1155.88 (719.13)	395.24 (270.34)	352.11 (172.14)	929.02 (450.07)	449.42 (234.81)	445.83 (284.68)
LABA n (%)	105 (99)	48 (100.0)	60 (100.0)	15 (100.0)	772 (94.8)	17 (100.0)	21 (100.0)	45 (100.0)	20 (100.0)	42 (97.7)	42 (100.0)
LAMA n (%)	61 (57.4)	8 (16.7)	12 (20)	0 (0.0)	315 (38.7)	7 (41.2)	10 (47.6)	20 (44.5)	6 (30)	25 (58.1)	4 (0.1)
LTRA n (%)	49 (46.2)	28 (58.3)	0 (0.0)	9 (60.0)	166 (20.4)	13 (76.5)	8 (38.1)	11 (24.4)	12 (60)	10 (23.2)	19 (45.2)

HR = Croatia; HU = Hungary; LT= Lithuania; LV = Latvia; NL = Netherlands; PL = Poland; RO = Romania; RS = Serbia; SE = Sweden; SI = Slovenia; TR = Turkey. BMI: Body Mass Index; FEV1: Forced Expiratory Volume in the 1st second; FVC: forced vital capacity; IgE: immunoglobulin E; FeNO: Fraction exhaled nitric oxide. OCS: oral corticosteroids; ACQ: Asthma Control Questionnaire, ICS: Inhaled corticosteroids; LABA: Long-acting beta-agonists; LAMA: Long-acting muscarinic antagonists; LTRA: Leukotriene receptor antagonists. *Packyears was calculated excluding non smokers (Packyears = 0). *Compliance was defined if answering the question "Has adherence ICS/OCS been checked in the last 12 months?". § Data on exacerbations were collected registering the numbers of the exacerbations reported by the patient in the previous 12 months.

In all countries, patients with severe asthma showed similar characteristics. Only Sweden and the Netherlands reported an equal percentage of non-smokers and ex-smokers (SE: 50% non-smokers and 50% ex-smokers; NL: 53.6% non smokers and 45.6% ex-smokers).
Most countries reported that patients had experienced between 2 and 5 exacerbations in the previous year, with the exception of Slovenia and Turkey where a relatively higher percentage of patients had experienced 0 or 1 exacerbation (SI: 67.6% and TR: 83.8%), and in Romania and Sweden, where 50% of patients had experienced between 0 and 1 exacerbation in the previous year. Overall, 277(22.5%) patients were using oral corticosteroids (OCS). Long acting muscarinic antagonists (LAMA) and leukotriene receptor antagonists (LTRA) were variably prescribed among countries.

The cohort was further characterized by co-morbidities that are known to be associated with asthma. The frequencies of the comorbidities were variable between countries (**table 2**). The most frequent being: allergic rhino conjunctivitis (the highest percentage registered in Poland (PL) 52.9%) chronic rhinosinusitis (the highest percentage reported in Hungary (HU) of 89.6% and in Croatia (HR) with 73.6%), nasal polyps (Hungary (HU) and Latvia (LV) reported the highest percentage of 62.5% and 53.3% respectively) and gastroesophageal reflux (GERD) mostly reported in Hungary (56.2%).

Table 2: Summary of comorbidities in patients with severe asthma included in SHARP Central.

	HR (n =106)	HU (n=48)	LT (n=60)	LV (n=15)	NL (n= 814)	PL (n=17)	RO (n=21)	RS (n=45)	SE (n=20)	SI (n=43)
Atopic dermatitis (%)	4 (3.8)	2 (4.2)	1 (1.7)	1 (6.7)	120 (14.7)	2 (11.8)	0 (0.0)	1 (2.2)	0 (0.0)	0 (0.0)
Allergic rhino conjunctivitis (%	29 (27.4)	12 (25.0)	11 (18.3)	6 (40.0)	154 (18.9)	9 (52.9)	1 (4.8)	8 (17.8)	1 (5.0)	1 (2.3)
Chronic rhinosinusitis (%)	78 (73.6)	43 (89.6)	16 (26.7)	9 (60.0)	487 (59.8)	10 (58.8)	11 (52.4)	21 (46.7)	8 (40.0)	3 (7.0)
Nasal polyps (%)	45 (42.5)	30 (62.5)	11 (18.3)	8 (53.3)	367 (45.1)	7 (41.2)	6 (28.6)	13 (28.9)	7 (35.0)	3 (7.0)
Aspirin intolerance (%)	18 (17.0)	10 (20.8)	3 (5.0)	3 (20.0)	91 (11.2)	3 (17.6)	3 (14.3)	1 (2.2)	2 (10.0)	3 (7.0)
Vocal cord dysfunction (%)	1 (0.9)	0 (0.0)	9 (15.0)	0 (0.0)	23 (2.8)	1 (5.9)	0 (0.0)	2 (4.4)	0 (0.0)	0 (0.0)
Panic hyperventilation (%)	1 (0.9)	5 (10.4)	2 (3.3)	0 (0.0)	73 (9.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Depression (%)	12 (11.3)	12 (25.0)	5 (8.3)	0 (0.0)	111 (13.6)	1 (5.9)	1 (4.8)	7 (15.6)	1 (5.0)	1 (2.3)
Gastroesophageal reflux (%)	29 (27.4)	27 (56.2)	15 (25.0)	2 (13.3)	174 (21.4)	5 (29.4)	4 (19.0)	13 (28.9)	2 (10.0)	4 (9.3)
Cardiac failure (%)	6 (5.7)	4 (8.3)	12 (20.0)	1 (6.7)	19 (2.3)	5 (29.4)	3 (14.3)	1 (2.2)	1 (5.0)	1 (2.3)
OSAS (%)	3 (2.8)	2 (4.2)	1 (1.7)	0 (0.0)	88 (10.8)	0 (0.0)	0 (0.0)	3 (6.7)	3 (15.0)	2 (4.7)
Bronchiectasis (%)	11 (10.4)	3 (6.2)	11 (18.3)	2 (13.3)	132 (16.2)	2 (11.8)	13 (61.9)	13 (28.9)	1 (5.0)	2 (4.7)

OSAS: Obstructive sleep apnea syndrome. *Turkish was not included because of the absence of information available at that moment on comorbidities.

Use of anti-IL5(R) biologics by SHARP Central registry patients

All three biologicals were prescribed among the ten countries, with mepolizumab being the most prescribed, and reslizumab the least (**table 3**), with the exception of Romania (RO) and Serbia (RS) where benralizumab was most prescribed (100% and 84.4%, respectively).

Table 3: Prescription of anti-IL-5(R) per country.

	Mepolizumab n (%)	Reslizumab n (%)	Benralizumab n (%)
HR	48 (45.3)	23 (21.7)	35 (33.0)
HU	31 (64.6)	<5	13 (27.1)
LT	51 (85.0)	0 (0.0)	9 (15.0)
LV	8 (53.3)	0 (0.0)	7 (46.7)
NL	521 (64.0)	113 (13.9)	182 (22.4)
PL	9 (52.9)	0 (0.0)	8 (47.1)
RO	0 (0.0)	0 (0.0)	21 (100.0)
RS	0 (0.0)	7 (15.6)	38 (84.4)
SE	17 (85.0)	<5	<5
SI	43 (100.0)	0 (0.0)	0 (0.0)*
TR	42 (100.0)	0 (0.0)	0 (0.0)

HR = Croatia; HU = Hungary; LT= Lithuania; LV = Latvia; NL = Netherlands; PL = Poland; RO = Romania; RS = Serbia; SE = Sweden; SI = Slovenia; TR = Turkey. Countries with information for less than 5 patients are reported "<5" for privacy. *Lack of data depending on the fact that SI at that time was still building the registry.

An overview of the number and the percentage missing data per variable is provided in the Supplementary Material (**table S1**). The overall number of missing data at baseline is 27%. The highest amount of missing information is reported for the Asthma Control Questionnaire score, which has been mainly reported by Dutch records. Moreover, the overview of comorbidities provided in table 2 is summarized considering 10 out of 11 countries because of missing data from the Turkish patients included in the SHARP CENTRAL Registry.

Comparison of patients from individual RCTs and those from the SHARP Central registry

10 RCTs studies were selected: 4 for mepolizumab[16–19], 3 for benralizumab [13–15] and 3 for reslizumab[10–12]. An overview of trials' eligibility criteria extracted from the study protocols is provided in the Supplementary Material (**table S2**). A summary of the results of the comparison between the trial population and the SHARP Central population anti-IL-5(R) starters is provided in **Supplementary tables S3-S5**. Furthermore, an additional comparison of the characteristics of the eligible patients per each biologic with the respective RCTs is represented in Supplementary tables S3.1-S4.1-S5.1. Significant differences were found between baseline characteristics of

patients included in the treatment-arm of mepolizumab, benralizumab and reslizumab trials and patients with severe asthma of SHARP Central registry with respect to both demographic (e.g. Age, gender) and clinical characteristics (e.g. inhalers usage and oral corticosteroids consumption). With the selection of only eligible patients those differences were much lower per treatment arm.

Assessment of eligibility of SHARP Central registry patients for inclusion in pre-registration anti-IL5(R) RCTs

Among SHARP Central registry, 991 (80.5%) patients not fulfilled the eligibility criteria of RCTs, whereas 240 (19.5 %) were considered eligible. 327 (26.56%) patients met the eligibility criteria of at least one of the selected trials (**figure 1**). After assessing eligibility by biologics, 24 (13.6%) patients were eligible for mepolizumab, 100 (56.8%) for benralizumab and 52 (29.5%) for reslizumab (**figure 2**). Overall, the major discrepancies characteristics between eligible and not eligible patients according inclusion and exclusion criteria with respect to the criteria were: high ICS dosage, ACQ score ≥ 1.5, pack years ≥ 10, better lung function and the presence of other respiratory or eosinophilic conditions, as it is shown in **figure 3**. The frequencies of reasons for ineligibility in each country are shown in **table 4**. A description of the distribution of comorbidities in eligible and not eligible patients is provided in the Supplementary material (**figure S2**); RCT-eligible patients in SHARP Central reported to have more frequently comorbidities such as chronic rhinosinusitis, nasal polyps and allergic rhinoconjunctivitis.

Table 4: Characteristics of patients with severe asthma included in SHARP Central, ineligible for Phase III RCTs.

	HR	HU	LT	LV	NL	PL	RO	RS	SE	SI	TR
N (%)	96 (90.5)	41 (85.4)	49 (81.6)	14 (93.3)	621 (58.7)	13 (76.5)	21 (100)	41 (91.2)	16 (80)	38 (88.4)	41 (97.6)
Smoking History											
Never n(%)	62 (64.6)	34 (82.3)	32 (65.3)	10 (71.4)	305 (49.1)	10 (76.92)	14 (66.7)	29 (70.7)	7 (43.7)	25 (65.8)	31 (75.6)
Ex n(%)	30 (31.2)	4 (9.8)	13 (26.5)	4 (28.6)	310 (49.9)	3 (23.1)	7 (33.3)	12 (29.3)	9 (56.2)	13 (34.2)	9 (21.9)
Active n(%)	4 (4.2)	3 (7.3)	4 (8.2)	0	6 (0.9)	0	0	0	0	0	1 (2.4)
Pack/year mean(SD)	22.6(14.4)	14.3(9.6)	14.9(11.4)	15.7(15.1)	15.5(14.5)	27.5(31.8)	20.4(13.3)	22.1(13.8)	9.3 (8.2)	21.7(18.3)	7.4 (8.8)
Bronchiectasis n(%)	11(11.4)	3(7)	11(22)	2(14)	132(21)	2(15)	13(61.9)	13(32)	1(6)	2(5)	n/a
EGPA n(%)	17(17.7)	0	2(4)	1(7)	36(5)	0	2(9)	0	2(12)	1(2)	n/a
Eosinophilic pneumonia n(%)	13(13.5)	3(7)	0	2(14)	50(8)	2(15)	1(4)	0	0	2(5.3)	n/a
ABPA n(%)	4(4.2)	0	0	0	14(2)	0	1(4.7)	0	1(6.2)	0	n/a
ACQ 5 mean(SD)	1.12 (1.15)	1.12 (0.66)	1.98 (1.34)	1.57 (1.06)	2.12 (1.14)	1.45 (0.82)	2.17 (NA)	n/a	1 (NA)	2 (NA)	1.33 (NA)
ICS (mcg/day) dose mean(SD)	354.2 (271.2)	468.5 (218.6)	707.2 (516.1)	314.5 (230.8)	753.8 (598.8)	988.4 (660.8)	395.2 (270.3)	351.7 (180.2)	845.2 (383.2)	413.1 (205.5)	451.8 (285.5)

EGPA: Eosinophilic granulomatosis with polyangitis; ABPA: Allergic bronchopulmonary aspergillosis; ACQ: Asthma Control Questionnaire; ICS: Inhaled corticosteroids. HR = Croatia; HU = Hungary; LT= Lithuania; LV = Latvia; NL = Netherlands; PL = Poland; RO = Romania; RS = Serbia; SE = Sweden; SI = Slovenia; TR = Turkey. n/a = not available

Comparison of countries across Europe showed significant differences between countries in concordance in inclusion/exclusion criteria between the patients for treatment in clinics and those enrolled in RCTs, with overall discordance being lowest in the NL (58.7%) and highest in RO (100%). A smoking history of ≥ 10 pack/years was the most common characteristic that would have made patients started on an anti-IL5 biologic ineligible by RCT criteria. All ineligible patients in all the countries reported at least one respiratory disease other than with severe asthma, with the highest overall number of patients registered in Romania (RO) (79.6%). The reported other respiratory diseases were: bronchiectasis (the highest number of patients registered in Romania (RO) (61.9%)), Eosinophilic granulomatosis with polyangitis (EGPA) mainly reported in Croatia (HR) 17.7% as well as eosinophilic pneumonia with 13.5% of patients and 17.1% of the patients reported Allergic bronchopulmonary aspergillosis (ABPA), mostly in Sweden (SE) with 6.2% of patients; 5 countries reported RCT-ineligible severe asthma patients according to Asthma Control score ≤ 1.5: Croatia (HR) with mean(SD) 1.12(1.15), Hungary (HU) with mean(SD) 1.12(0.66), Poland (PL) with mean(SD) 1.45(0.82), Sweden (SE) with mean(SD) 1(NA) and Turkey with mean(SD) 1.33(NA). In all countries the RCT-ineligible patients received a lower dose of inhaled corticosteroids (ICS) compared to trials with the lowest dose registered in Latvia (mean (SD) 314.5(230.8) mcg/day).

Discussion

This study shows that characteristics of patients who received biological treatment for severe asthma in real-life differed from country to country in terms of smoking history, clinical characteristics (ACQ-5 score, number of exacerbations in the previous year, comorbidities) and medication use (OCS, LAMA, LTRA). The characteristics of severe asthma patients included in the SHARP CENTRAL Registry differed from the characteristics of patients enrolled in phase III RCTs of anti-IL-5(R) therapies. The main discrepancies between patients treated in the real world and those in RCTs were the higher number of pack years smoked, concomitant non-asthma related respiratory or eosinophilic diseases, lower maintenance dose of ICS and lower ACQ score in the real-world patients. Thus, a large proportion of patients in the SHARP CENTRAL registry would not have been eligible for anti-IL-5(R) treatment if the in- and exclusion criteria of the RCTs had been followed.

The present study confirms and extends the results from a recent study by Richards and colleagues[6], who showed that 119 patients from the Dutch severe asthma registry received treatment with mepolizumab, although they would normally have been excluded from clinical trials because of heavy smoking in the past, severe comorbidities, hypereosinophilic syndromes or fixed airway obstruction.
Trial eligibility in a real-life severe asthma cohort was also assessed by Brown and colleagues[20] who selected data from the Wessex Severe Asthma Cohort (WSAC) and compared these with 37 RCTs evaluating 20 biological therapies. They found that only 9.8% (in a range between 3.5% - 17.5%) of patients would have been eligible for inclusion in trials investigating anti-IL-5 treatment. In line with our results, 26% of severe asthmatics in their study were current smokers or ex-smokers with a smoking history of ≥ 10 pack-years and were considered ineligible for RCTs even if they reported high blood or sputum eosinophils counts.
Another study[21], identified the most frequent causes for exclusion from RCTs in asthma patients. These included comorbidities such as anxiety and depression (3.3%), arrhythmias (2.3%), coronary artery disease (1.2%), active smoking (34.3% of the population) and lung diseases other than asthma (5%). Notably, our analyses show that in real life these patients are not excluded for anti-IL-5(Ra) therapy as shown in table 2.

Several studies have already shown that anti-IL5(R) biologics can be efficacious in patients with severe asthma who do not fulfil the strict criteria of the Phase III RCTs. In particular, have these treatments been proven to be effective in severe asthma patients with other respiratory diseases, or patients with a concomitant hypereosinophilic disease. A recent single-centre study[22] showed that mepolizumab improved symptoms control (Asthma Control Test (ACT) score ACT from a mean(SD) of 13 (4.8) to 20.7 (4.6)), reduced asthma exacerbation and OCS use in patients with coexistent severe asthma and bronchiectasis after 6 months of treatment.

Also patients with Eosinophilic granulomatosis and Polyangiitis (EGPA) and Hypereosinophilic syndrome (HES) have been shown to benefit from anti-IL-5 treatments. Two studies reported relevant steroid-sparing effect of reslizumab and benralizumab for severe asthma patients with EGPA[23, 24] and a RCT double-blind phase III trial of 136 participants reported in addition an improvement in the disease remission with mepolizumab at the dosage of 300 mg[25]. In fact, the European Medicine Agency (EMA) already approved mepolizumab as an add-on treatment for patients with EGPA. In patients with HES, mepolizumab significantly reduced the occurrence of flares in a phase III RCT, and is now the first and only biologic FDA approved treatment for this rare group of serious eosinophilic diseases. In addition, according to robust real-word evidence, "asthma tailored" mepolizumab 100 mg is able to maintain EGPA remission and to exerting at the same time a significant steroid sparing effect in patient with persisting severe eosinophilic asthma after the systemic disease resolution[26–28]. Since not all eosinophilic diseases are sensitive to anti IL5(R) biologics, further research is needed in order to identify new potential phenotypes and endotypes [29] for better classification of patients with eosinophilic airway disease. This will allow us to assess whether a patient with eosinophilic airway disease will benefit from treatment with an anti-IL-5(R) biologic or not.

A common difference between patients who receive specific treatment in real-life and those who participate in RCTs is age. Previous studies [4, 6] in patients with severe asthma have shown that the mean age of patients enrolled in clinical trials is lower than the age of patients represented in clinical registries. This might be explained by the fact that elderly patients with severe asthma are excluded from phase III RCTs because their airways may have undergone age-related structural, functional and immunological changes[30], which could potentially reduce the response to biologic therapies. However, in our study, we did not observe any age differences between countries, nor did it appear to be a relevant characteristic of non-eligibility. This is in line with the results of a meta-analysis anti IL-5(Ra) RCTs, showing that age does not negatively affect the efficacy of these monoclonal antibodies. Thus, the use of these biologicals could also be extended to a frail population[31, 32]. The same findings were recently confirmed by a real-life analysis focusing on clinical response of mepolizumab and omalizumab in different genders and age ranges [33].

Our study has several clinical and research implications. First, it shows once again the importance of collecting real-world data and comparing it with data from phase III RCTs. Our findings show that the real-life severe asthma population appears to be different from the populations in clinical trials, and suggests that a broader population than the one represented in clinical trials could profit from anti-IL-5 treatment. Not only patients with multiple comorbidities, whether or not related to asthma, but also the elderly, the heavy smokers, and patients with airway remodelling appear to benefit from this treatment. Second, our study emphasizes the importance of a long-term registration of data from patients with chronic conditions such as severe asthma who are receiving new

treatments. Without such data collection and privacy-proof storage it would not be possible to get an impression of the real-life efficiency of this biological therapy. Third, our study enlightens the importance of harmonizing data and unifying national registries in order to reduce differences in management practice in different countries and extend the knowledge of severe asthma across Europe.

Apart from SHARP Central, several other active projects are collecting real-life data from severe asthma patients on a large scale, such as the International Severe Asthma Registry (ISAR) project and the on going 3TR pan-European consortium[34, 35]. Like SHARP Central, these multinational programs will hopefully contribute to a better characterization and understanding of the complexities of severe asthma. The discrepancies between RCTs and real-life registries observed in our study may already provide an important source of inspiration for identifying novel mechanisms and treatment targets not only for patients with severe asthma but also for patients with a variety of type-2 inflammatory diseases.

Our study has several strengths and a few limitations. First, to our knowledge, our study is the first to have used data from clinical care facilities from 11 different European countries to characterize patients with severe asthma who were prescribed anti-IL-5(Ra) biologics in real life, and to investigate differences in prescription practices between countries. Second, it is unique that for this study 11 different countries used disease registries with an identical data model and treating physicians entered patient data via an e-CRF translated into 11 different languages. As a result, there was no bias due to incorrect data harmonization. Potential limitations of this study include first that our results represent a snap shot, which may change over time, since collection of data in the SHARP central registry is still on going. Yet, we were able to select more than 1000 patients from 11 different European countries, so we believe the population to be quite representative of the actual real-life clinical care setting. Second, we lacked reliable data in the SHARP central registry about the exact frequency of exacerbations, which was an inclusion criterion in many RCTs. However, we believe that the use of frequency categories (0-1, 2-5, >5) did not influence the interpretation of our results. Third, there were quite a few missing data, which is unavoidable in clinical registries that are not closely monitored. Fourth, there were differences between countries in patient numbers. Small numbers or multiple missing data may have led to overestimation of differences in quantitative data like age or BMI, but not in qualitative data like smoking history or comorbidities. Lastly, we could not include the same information per each trial when we compared baseline characteristics of SHARP Central patients and RCTs. This is due to the fact that we do not have access to the original raw data of previously published RCTs. Furthermore, each variable in SHARP Central might have been retrieved in a different way than the ones in RCTs (e.g. exacerbations previously explained). Therefore, we could only present comparison of data we were sure could have been retrieved in the same way as in SHARP Central registry. Even though this information might be considered

incomplete, it is an important “first-step” to understand the discrepancies in real-life population with RCTs.

In conclusion, we have demonstrated that patients receiving asthma biologics in routine clinical asthma care, in a wide European spectrum, differs from patients who participation in phase III RCTs. The population benefiting from these drugs in real-life is much more diverse and broader than the population enrolled in RCTs. Future research should focus on gathering more patient-level data in a longitudinal long-term setting, to evaluate whether the population considered ineligible in randomized trials, might derive genuine benefits from anti-IL-5 treatment comparable to those already reported in clinical trials. This study demonstrates the importance of real life cohorts in describing the efficacy of biologics in a broader population of patients with severe asthma.

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Conflict of interest

Stefania Principe declares to be employed by the University of Palermo with a co-EU research funds EU-REACT *FESR o FSE, PON Ricerca e Innovazione 2014-2020 - DM 1062/2021*. Prof. Dr. Celeste Porsbjerg declares, in the past 36 months, grants from AZ, GSK, Novartis, TEVA, Sanofi, Chiesi, ALK, consulting fees from AZ, GSK, Novartis, TEVA, Sanofi, Chiesi, ALK, honoraria for lectures from AZ, GSK, Novartis, TEVA, Sanofi, Chiesi, ALK, participation for advisory boards AZ, GSK, Novartis, TEVA, Sanofi, Chiesi, ALK. Dr. Sabina Skgrat declares, in the past 36 months, honoraria for lectures and educational events from Astra Zeneca, Pliva Teva, Berlin Chemie and Chiesi, Medis. And participation to advisory boards AZ, Berlin Chemie. Dr. ten Brinke reports grants from AstraZeneca, GSK, TEVA, fees for advisory boards and lectures from AstraZeneca, GSK, Novartis, TEVA, Sanofi Genzyme. Dr. Sanja-Popović-Grle declares consulting fees from AZ, GSK, Novartis, Pliva TEVA, Sanofi, ALK and honoraria for lectures from AZ, GSK, Novartis, Pliva TEVA, Sanofi, ALK. Dr. Ineta Grisle declares honoraria for lectures from AZ, Novartis, GSK, Berlin-Chemie, Boerinher- Ingelheim, Norameda. Dr. Piotr Kuna declares honoraria for lectures/presentations from AstraZeneca, GSK, Boehringer Ingelheim, Berlin Chemie Menarini, FAES, Adamed, Polpharma, Glenmark, Novartis, Teva, and support for attending meetings from AstraZeneca, Berlin Chemie, Menarini. All the other authors declare that they have no conflicts of interest.

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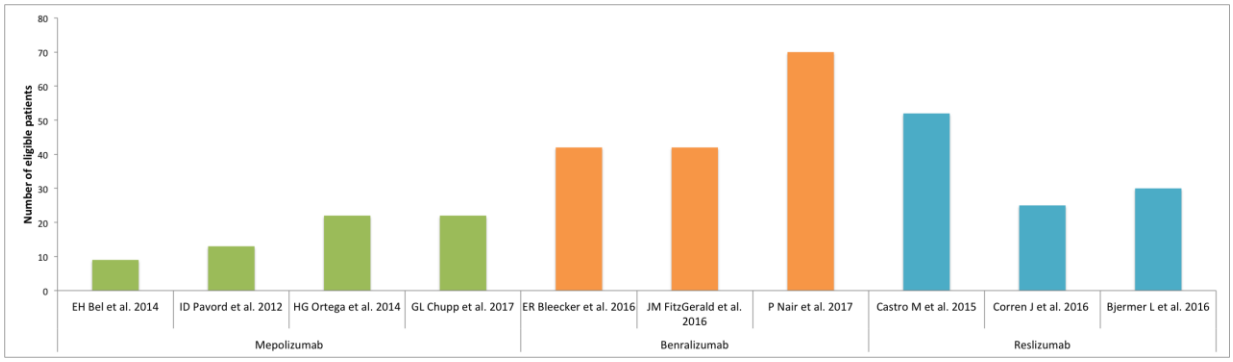

Figure 1: distribution of the eligibility per trial for severe asthma patients in SHARP following inclusion/exclusion criteria of the selected trials

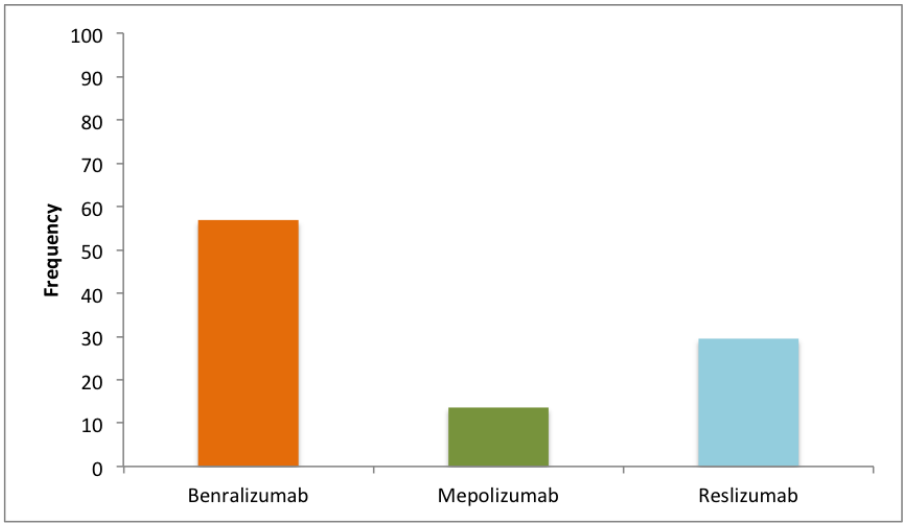

Figure 2: treatment eligibility stratifying per biologic therapy.

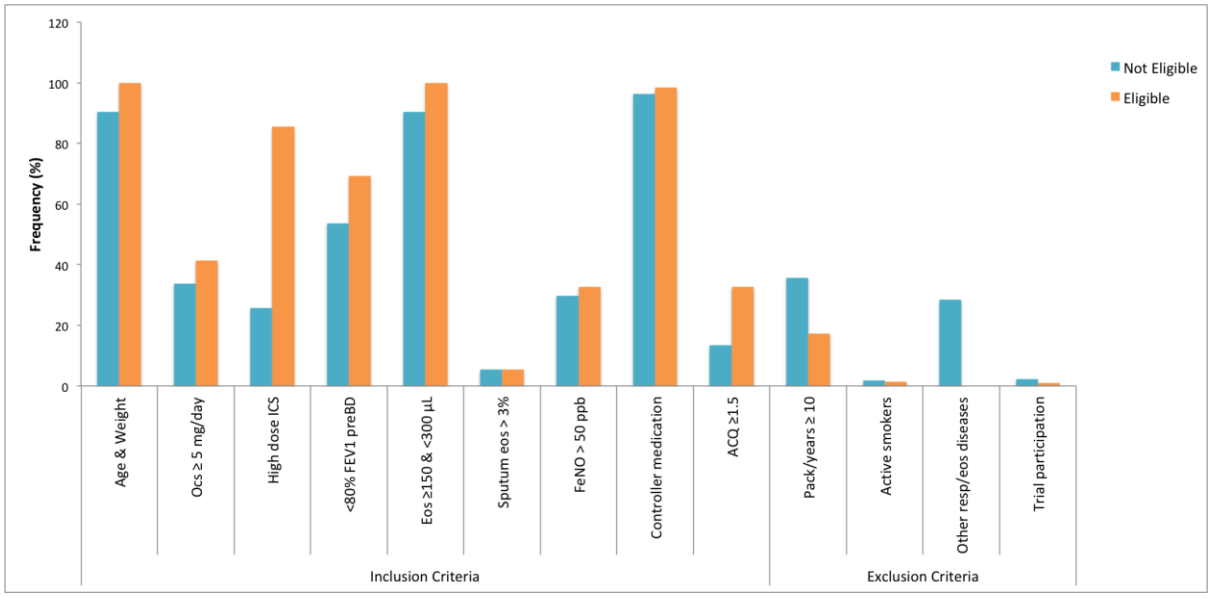

Figure 3: overall distribution of the severe asthma SHARP patients according to trials' eligibility. Trial ineligibility was defined as: fulfilling at least one of the exclusion criteria stated in the selected RCTs; or not fulfilling one of more of the inclusion criteria stated in RCTs of the patient prescribed one of the biologicals

Characteristics of severe asthma patients on biologics; a real-life European registry study

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Supplementary Material

Table S1: missing variables in SHARP Central registry

	Number of missing	Percentage of missing
Trial participation (n)	152	12.3
Age (yrs)	3	0.2
Smoking History	1	0.08
Pack years	28	5.5
BMI	155	12.6
History of Frequent respiratory infections n(%)	146	11.9
Bronchiectasis	148	12.0
EGPA	145	11.8
Eosinophilic pneumonia	147	11.9
ABPA	146	11.9
OCS dosage	1	0.08
FEV1 preBD (%)	98	8.0
FVC preBD(%)	102	8.3

FEV1/FVC preBD (%)	186	15.1
Eosinophils (cell/µL)	24	1.9
FeNO (ppb)	285	23.1
ACQ 5	852	69.2

Figure S1: flow chart of the literature selection of RCTs for the evaluation of the main inclusion/exclusion criteria[1–10].

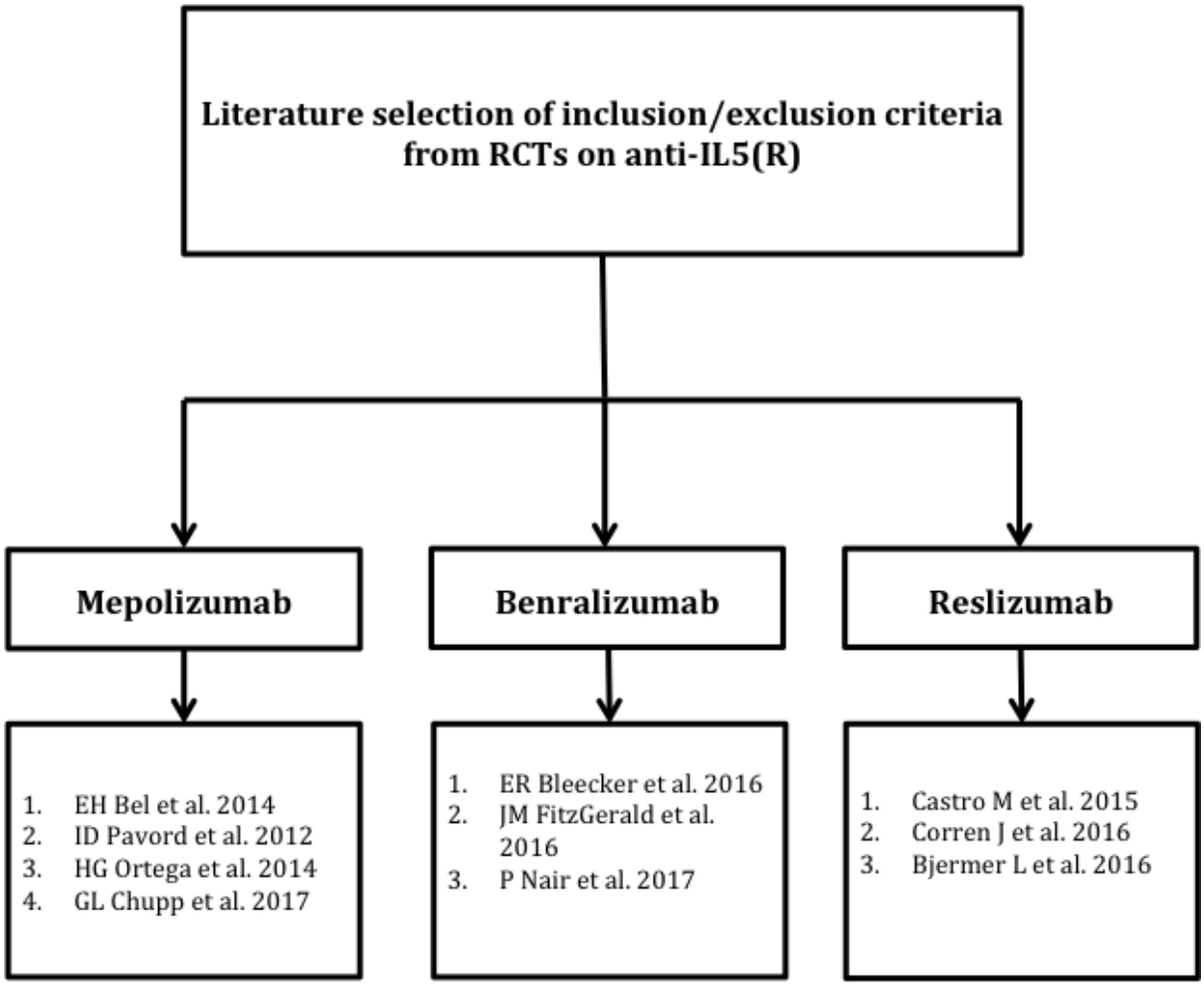


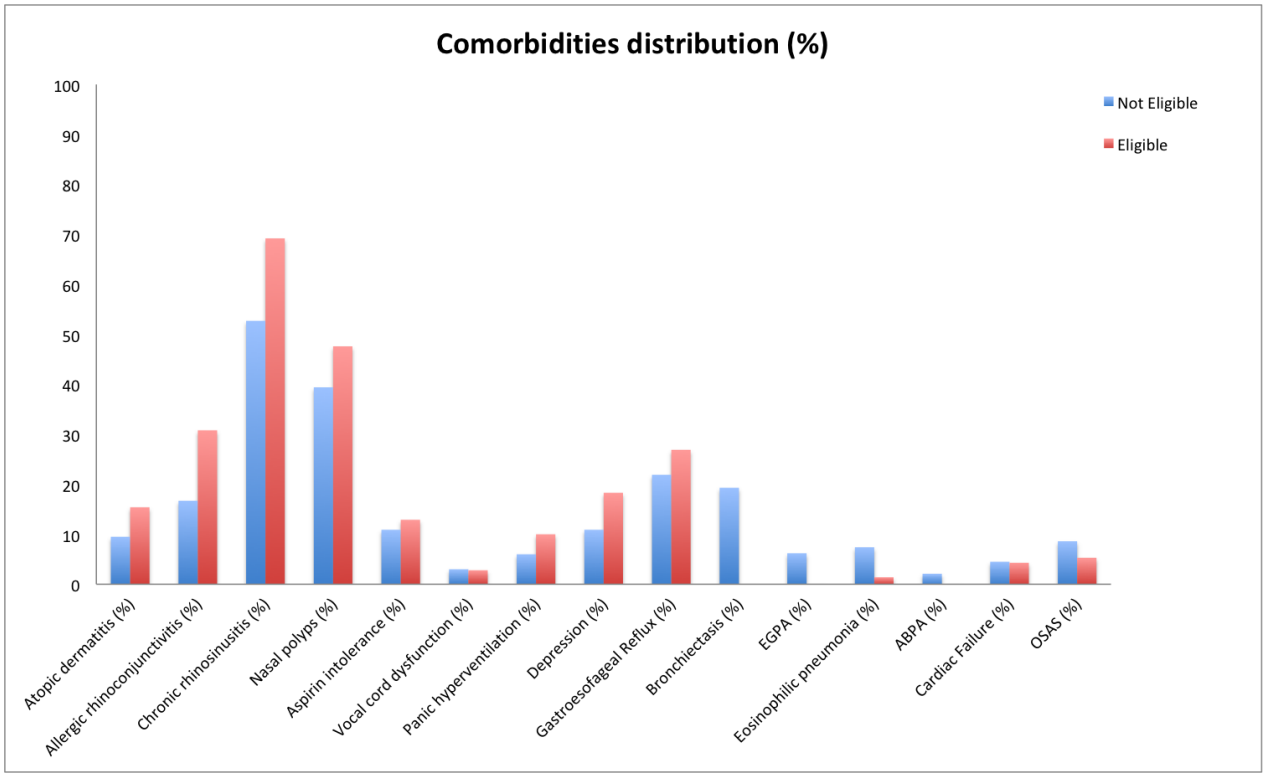
Table S2: List of trials' inclusion/exclusion criteria for the assessment of ineligibility[1–10].

	Mepolizumab				Benralizumab			Reslizumab		
Inclusion criteria	**DREAM**	**SIRIUS**	**MENSA**	**MUSCA**	**SIROCCO**	**CALIMA**	**ZONDA**	**Castro M (2015)**	**Corren J (2016)**	**Bjermer L (2016)**
Age ≥ 18 years to 65 years							▯		▯	
Age ≥ 12 years to 75 years	▯	▯	▯	▯	▯	▯		▯		▯
Systemic Corticosteroids: Requirement for regular treatment with maintenance systemic corticosteroids (prednisone or equivalent)		▯					▯			
Inhaled Corticosteroids: High dose ICS usage	▯	▯	▯	▯	▯	▯	▯	▯	▯	▯
FEV1: Persistent airflow obstruction as indicated by a pre-bronchodilator FEV1 <80% predicted.	▯	▯			▯		▯			
Eosinophilic Asthma: Prior documentation of eosinophilic asthma or high likelihood of eosinophilic asthma.	▯	▯	▯	▯	▯	▯	▯	▯		▯
Compliance: related to inhaler therapy, OCS assumption, asthma daily diary							▯			
Controller Medication: Usage of controller-medication (current usage of LABA, LTRA or theophylline for at least 3 months)	▯	▯	▯	▯	▯	▯				
At least 1 documented asthma exacerbation in the previous 12 months prior to the date informed consent is obtained	▯						▯	▯		
ACQ score of at least 1.5.					▯			▯	▯	▯
Weight: > 45 kg	▯	▯	▯	▯	▯					
Asthma: Evidence of asthma indicated by airway reversibility, hyperresponsiveness or airway variability.	▯	▯	▯	▯			▯	▯	▯	▯
Exclusion criteria										
Smoking history: Current smokers or former smokers (> 6 months)	▯	▯	▯	▯	▯	▯	▯	▯	▯	
Concurrent Respiratory Disease: Presence of a clinically important lung condition other than asthma.	▯	▯	▯	▯	▯	▯	▯	▯	▯	▯
Malignancy: A current malignancy or previous history of cancer in remission for less than 12 months prior screening		▯	▯	▯						

Liver Disease: Unstable liver disease		▯	▯	▯	▯	▯	▯			
Cardiovascular: Subjects who have severe or clinically significant cardiovascular disease uncontrolled with standard treatment.		▯	▯	▯	▯	▯	▯			
Other Concurrent Medical Conditions: Subjects who have known, pre-existing, clinically significant endocrine, autoimmune, metabolic, neurological, renal, gastrointestinal, hepatic, haematological or any other system abnormalities that are uncontrolled with standard treatment.	▯	▯	▯	▯	▯	▯	▯	▯	▯	▯
Eosinophilic Diseases: Subjects with other conditions that could lead to elevated eosinophils such as Hypereosiniophilic Syndromes, including Churg-Strauss Syndrome, or Eosinophilic Esophaghitis. Subjects with a known, pre-existing parasitic infestation within 6 months prior to Visit 1 are also to be excluded.	▯	▯	▯	▯	▯	▯	▯	▯	▯	▯
Immunodeficiency: A known immunodeficiency (e.g. human immunodeficiency virus - HIV), other than that explained by the use of corticosteroids taken as therapy for asthma.	▯	▯	▯	▯				▯	▯	▯
Other Monoclonal Antibodies: Subjects who have received any monoclonal antibody (other than Xolair)	▯	▯	▯	▯				▯	▯	▯
Investigational Medications: Subjects who have received treatment with an investigational drug within the past 30 days or with other investigational biologics	▯	▯	▯	▯				▯	▯	
Pregnancy: Subjects who are pregnant or breastfeeding.	▯	▯	▯	▯				▯	▯	▯
Hypersensitivity: Subjects with a known allergy or intolerance to a monoclonal antibody or biologic.	▯	▯	▯	▯						
Alcohol/Substance Abuse: A history (or suspected history) of alcohol misuse or substance abuse within 2 years		▯	▯	▯						
Adherence: Subjects who have known evidence of lack of adherence to controller	▯	▯	▯	▯						▯

medications and/or ability to follow physician's recommendations.										
Acute upper or lower respiratory infections	▯				▯	▯	▯	▯		▯
Patient is currently using systemic corticosteroids (includes use of oral corticosteroids).	▯								▯	▯
Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) level ≥2.5 times the upper limit of normal (ULN) confirmed during screening period							▯			
The patient has presence of or suspected parasitic infestation/infection.	▯								▯	
Patients may not have received any live attenuated vaccine within the 12-week period before study entry.									▯	

Figure S2: Comorbidities distribution in the eligible and not eligible severe asthma anti-IL5(R) starters in SHARP Central. EGPA: Eosinophilic granulomatosis with polyangitis; ABPA: Allergic bronchopulmonary aspergillosis; OSAS: Obstructive sleep apnea syndrome.


Comorbidities distribution (%)
100
90
80
70
60
50
40
30
20
10
0
Not Eligible
Eligible
Atopic dermatitis (%)
Allergic rhinoconjunctivitis (%)
Chronic rhinosinusitis (%)
Nasal polyps (%)
Aspirin intolerance (%)
Vocal cord dysfunction (%)
Panic hyperventilation (%)
Depression (%)
Gastroesofageal Reflux (%)
Bronchiectasis (%)
EGPA (%)
Eosinophilic pneumonia (%)
ABPA (%)
Cardiac Failure (%)
OSAS (%)

Comparison of baseline severe eosinophilic asthma patients' characteristics commenced on anti-IL5(R) and baseline characteristics of severe eosinophilic asthma patients recruited in RCTs

Table S3: Comparison between patients' characteristics from mepolizumab trials and SHARP. BMI: Body Mass Index; OCS: oral corticosteroids; FEV1: Forced Expiratory Volume in the 1st second; preBD: pre-bronchodilator; FVC: forced vital capacity; ACQ: Asthma Control Questionnaire; LABA: Long-acting beta-agonists; LAMA: Long-acting muscarinic antagonists; LTRA: Leukotriene receptor antagonists. § p or q value < 0.05.

	Mepolizumab				SHARP
	SIRIUS	DREAM	MENSA	MUSCA	
N	135	616	576	551	1231
Age mean (SD)	49.9 (12.34)	48.6 (11.28)§	50.1 (14.28)§	51(13.52)§	56.5(13.20)
Gender (F n)	74	387	329§	325§	602
BMI mean(SD)	28.66 (6.01)§	28.5(5.95)§	27.77(5.83)	28.2 (6.4)§	27.8 (5.49)
OCS (mg) mean(SD)	12.8 (6.73)§	17.4 (16.77)§	13.2 (11.89)§	13.0 (10.84)§	4.78 (8.87)
FEV1 preBD(L) mean(SD)	1.89 (0.75)	1.88 (0.66)§	1.82 (0.67)§	1.74 (0.62)§	2.21 (0.87)
FEV1 preBD (%) mean(SD)	57 (18.1)§	57.7(15.8)§	56.7(15.48)§	55.4(14.46)§	72.95 (22.11)
FEV1/FVC preBD(L) mean(SD)	0.61(0.12)	0.63(0.14)	0.63(0.12)	0.58 (0.11)	0.60 (0.13)
ACQ 5 mean (SD)	2.07(1.22)	2.35(1.05)	2.22(1.20)	2.19(1.13)	1.96 (1.22)
LABA (n (%))	21 (15.6) §	590 (95.8)	85 (14.8) §	547 (99.3)§	1187 (94.4)
LAMA (n (%))	26 (19.3)	45 (7.3) §	85 (14.8)§	114 (20.7)	468 (38)
LTRA (n (%))	57 (42.2)§	160 (26)	280 (48.6)§	222 (40.3)	325 (26.4)

Table S3.1: Comparison between patients' characteristics from mepolizumab trials and eligible mepolizumab starters in SHARP Central. BMI: Body Mass Index; OCS: oral corticosteroids; FEV1: Forced Expiratory Volume in the 1st second; preBD: pre-bronchodilator; FVC: forced vital capacity; ACQ: Asthma Control Questionnaire; LABA: Long-acting beta-agonists; LAMA: Long-acting muscarinic antagonists; LTRA: Leukotriene receptor antagonists. § p or q value < 0.05.

	Mepolizumab				SHARP Mepolizumab eligible
	SIRIUS	DREAM	MENSA	MUSCA	
N	135	616	576	551	24
Age mean (SD)	49.9 (12.34)	48.6 (11.28)	50.1 (14.28)§	51(13.52)§	49.9 (13.4)
Gender (F n)	74	387§	329	325§	13
BMI mean(SD)	28.66 (6.01)	28.5(5.95)	27.77(5.83)	28.2 (6.4)	28.3 (4.14)
OCS (mg) mean(SD)	12.8 (6.73)§	17.4 (16.77)§	13.2 (11.89)§	13.0 (10.84)§	7.54 (6.02)
FEV1 preBD(L) mean(SD)	1.89 (0.75)§	1.88 (0.66)§	1.82 (0.67)§	1.74 (0.62)§	2.10 (0.85)
FEV1 preBD (%) mean(SD)	57 (18.1)§	57.7(15.8)§	56.7(15.48)§	55.4(14.46)§	68.2(25.31)
FEV1/FVC preBD(L) mean(SD)	0.61(0.12)	0.63(0.14)	0.63(0.12)	0.58 (0.11)§	0.60 (0.14)
ACQ 5 mean (SD)	2.07(1.22)	2.35(1.05)§	2.22(1.20)	2.19(1.13)	2.26 (1.16)
LABA (n (%))	21 (15.6)§	590 (95.8)	85 (14.8) §	547 (99.3)	24 (100.0)
LAMA (n (%))	26 (19.3)	45 (7.3) §	85 (14.8)§	114 (20.7)	8 (33.4)
LTRA (n (%))	57 (42.2)	160 (26)	280 (48.6)§	222 (40.3)	5 (20.8)

Table S4: Comparison between patients' characteristics from benralizumab trials and SHARP. BMI: Body Mass Index; FEV1: Forced Expiratory Volume in the 1st second; preBD: pre-bronchodilator; ACQ: Asthma Control Questionnaire; LABA: Long-acting beta-agonists; LAMA: Long-acting muscarinic antagonists; LTRA: Leukotriene receptor antagonists. § p or q value < 0.05.

	Benralizumab			SHARP
	SIROCCO	CALIMA	ZONDA	
N	1204	1306	220	1231
Age mean (SD)	48.8 (14.03)§	49.3(14.4)§	51(11.3)	56.5(13.20)
Gender (M/F)	408/796§	499/807	85/135§	602/629
BMI mean(SD)	28.8(6.8)§	28.8(6.6)§	29.6(6.2)§	27.8 (5.49)
FEV1 preBD(L) mean(SD)	1.66 (0.57)§	1.76(0.63)§	1.85 (0.68)	2.21 (0.87)
FEV1 preBD (%) mean(SD)	56.7(14.6)§	58.3(14.9)§	59.5(17.5)§	72.95 (22.11)
FEV1/FVC preBD (%) mean(SD)	61(13)§	61(13)§	60(13)§	71.98(24.77)
ACQ 5 mean (SD)	2.81(0.93)§	2.71(0.92)§	2.6(1.1)	1.96 (1.22)
LABA (n (%))	1204 (100)	1300 (99.5)	NA	1187 (94.4)
LAMA (n (%))	101 (8.4)§	106 (8.1)§	NA	468 (38)
LTRA (n (%))	431 (35.8)	363 (27.8)	82 (37.3)§	325 (26.4)

Table S4.1: Comparison between patients' characteristics from benralizumab trials and eligible Benralizumab starters in SHARP Central. BMI: Body Mass Index; FEV1: Forced Expiratory Volume in the 1st second; preBD: pre-bronchodilator; ACQ: Asthma Control Questionnaire; LABA: Long-acting beta-agonists; LAMA: Long-acting muscarinic antagonists; LTRA: Leukotriene receptor antagonists. § p or q value < 0.05.

	Benralizumab			SHARP Benralizumab eligible
	SIROCCO	CALIMA	ZONDA	
N	1204	1306	220	100
Age mean (SD)	48.8 (14.03)	49.3(14.4)	51(11.3)	50.7(16.32)
Gender (M/F)	408/796	499/807	85/135	20/80
BMI mean(SD)	28.8(6.8)	28.8(6.6)	29.6(6.2)	28.0(5.37)
FEV1 preBD(L) mean(SD)	1.66 (0.57)	1.76(0.63)	1.85 (0.68)	1.80 (0.59)
FEV1 preBD (%) mean(SD)	56.7(14.6)	58.3(14.9)	59.5(17.5)	56.9 (14.70)
FEV1/FVC preBD (%) mean(SD)	61(13)§	61(13)§	60(13)§	54.64(11.87)
ACQ 5 mean (SD)	2.81(0.93)	2.71(0.92)	2.6(1.1)	2.37 (1.42)
LABA (n (%))	1204 (100)	1300 (99.5)	NA	97 (97)
LAMA (n (%))	101 (8.4)§	106 (8.1)§	NA	61 (61)
LTRA (n (%))	431 (35.8)	363 (27.8)	82 (37.3)§	43 (43)

Table S5: Comparison between patients' characteristics from benralizumab trials and SHARP. BMI: Body Mass Index; FEV1: Forced Expiratory Volume in the 1st second; preBD: pre-bronchodilator; ACQ: Asthma Control Questionnaire; ICS: Inhaled corticosteroids; LABA: Long-acting beta-agonists. § p or q value < 0.05.

	Reslizumab			SHARP
	Castro M	Corren J	Bjermer	
N	953	496	315	1231
Age mean (SD)	46.8 (14)§	44.9 (12.27)§	43.9 (14.42)§	56.5(13.20)
Gender (M/F)	356/597	181/315	132/183§	602/629
BMI mean(SD)	27.5 (5.7)	32.2 (8.33)§	27.6 (6.51)	27.8 (5.49)
FEV1 preBD(L) mean(SD)	1.99(0.75)§	2.12 (0.68)	NA	2.21 (0.87)
FEV1 preBD (%) mean(SD)	66.7(19.7)	66.7(16.1)	NA	72.95 (22.11)
ACQ 5 mean (SD)	2.65(0.85)§	2.56(0.69)§	NA	1.96 (1.22)
Blood eosinophils (cell/mcL) mean(SD)	654(629)	280(240.1)	NA	320.1 (259.58)
ICS dose (mcg/day) mean(SD)	821.5(436.7)	NA	NA	774.8 (621.3)
LABA (n (%))	803 (84.3)§	387 (78) §	245 (77.8) §	1187 (94.4)

Table S5.1: Comparison between patients' characteristics from reslizumab trials and eligible reslizumab starters in SHARP Central. BMI: Body Mass Index; FEV1: Forced Expiratory Volume in the 1st second; preBD: pre-bronchodilator; ACQ: Asthma Control Questionnaire; ICS: Inhaled corticosteroids; LABA: Long-acting beta-agonists. § p or q value < 0.05.

	Reslizumab			SHARP Reslizumab eligible
	Castro M	Corren J	Bjermer	
N	953	496	315	52
Age mean (SD)	46.8 (14)§	44.9 (12.27)§	43.9 (14.42)§	53.2(12.56)
Gender (M/F)	356/597	181/315	132/183§	29/23
BMI mean(SD)	27.5 (5.7)	32.2 (8.33)§	27.6 (6.51)	28.2 (5.33)
FEV1 preBD(L) mean(SD)	1.99(0.75)§	2.12 (0.68)	NA	2.24 (0.87)
FEV1 preBD (%) mean(SD)	66.7(19.7)§	66.7(16.1)§	NA	72.84 (23.05)
ACQ 5 mean (SD)	2.65(0.85)§	2.56(0.69)	NA	2.16 (1.36)
Blood eosinophils (cell/mcL) mean(SD)	654(629)	280(240.1)§	NA	731.6 (434.71)
ICS dose (mcg/day) mean(SD)	821.5(436.7)§	NA	NA	1473.2 (622.9)
LABA (n (%))	803 (84.3)§	387 (78) §	245 (77.8) §	52 (100)

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