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Principe, S.; Richards, L.B.; Hashimoto, S.; Kroes, J.A.; Bragt, J.J.M.H. van; Vijverberg, S.J.; ... ; SHARP Clinical Res Collaboration

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Stefania Principe[1,2], Levi B. Richards[1], Simone Hashimoto[1], Johannes Anthon Kroes[3], Job J.M.H. Van Bragt[1], Susanne J. Vijverberg[1], Jacob K. Sont[4], Nicola Scichilone[2], Kristina Bieksiene[5], Anneke Ten Brinke[6], Zsuzsanna Csoma[7], Barbro Dahlén[8], Bilun Gemicioglu[9], Ineta Grisle[10], Piotr Kuna[11], Zorica Lazic[12], Florin Mihaltan[13], Sanja Popović-Grle[14], Sabina Škrgat[15], Alessandro Marcon[16], Marco Caminati[17], Ratko Djukanovic[18], Celeste Porsbjerg[19] and Anke-Hilse Maitland Van Der Zee[1,20,21] on behalf of the SHARP Clinical Research Collaboration

[1]Amsterdam UMC University of Amsterdam, Department of Pulmonary Medicine, Amsterdam, the Netherlands. [2]University of Palermo, Department of Pulmonology, AOUP Policlinico "Paolo Giaccone", Palermo, Italy. [3]Department of Clinical Pharmacy and Pharmacology, Medical Centre Leeuwarden, Leeuwarden, Netherlands. [4]Department of Biomedical Data Sciences, Section Medical Decision Making, Leiden University Medical Centre, Leiden, Netherlands. [5]Department of Pulmonology, Lithuanian University of Health Sciences, Kaunas, Lithuania. [6]Medical Centre Leeuwarden, Leeuwarden, Netherlands. [7]National Koranyi Institute for Pulmonology, Budapest, Hungary. [8]Karolinska Institutet, Stockholm, Sweden. [9]Department of Pulmonary Diseases, Cerrahpasa Faculty of Medicine, Istanbul University-Cerrahpasa, Istanbul, Turkey. [10]Riga East University Hospital, Riga, Latvia. [11]Medical University of Lodz, Łódź, Poland. [12]University Clinical Center Kragujevac, Kragujevac, Serbia. [13]National Institute of Pneumology, Bucharest, Romania. [14]University Hospital Centre Zagreb, KBCZ Clinical Center for Pulmonary Diseases Jordanovac, Zagreb, Croatia. [15]Department of Pulmonary Diseases and Allergy, University Medical Centre Ljubljana, Medical Faculty, University of Ljubljana, Ljubljana, Slovenia. [16]Unit of Epidemiology and Medical Statistics, Department of Diagnostics and Public Health, University of Verona, Verona, Italy. [17]Department of Medicine, University of Verona and Verona University Hospital, Verona, Italy. [18]School of Clinical and Experimental Sciences, University of Southampton, National Institute for Health and Care Research, NIHR Southampton Biomedical Research Center, Southampton, UK. [19]Respiratory Research Unit, Bispebjerg University Hospital, Copenhagen, Denmark. [20]Amsterdam Institute for Infection and Immunity, Amsterdam, the Netherlands. [21]Amsterdam Public Health, Amsterdam, the Netherlands.

Corresponding author: Anke-Hilse Maitland van der Zee (a.h.maitland@amc.nl)

Shareable abstract (@ERSpublications)
The European severe asthma population that starts anti-IL5(R) is broader than represented in RCTs. Centralising clinical real-life registries is an important way to align the management and assessment of the disease. https://bit.ly/3y8optX

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Abstract

Background The use of anti-interleukin-5 (IL5) for severe asthma is based on criteria from randomised controlled trials (RCTs), but in real-life patients might not fulfil the eligibility criteria but may benefit from biologics. We aimed to characterise patients starting anti-IL5(R) in Europe and evaluate the discrepancies between initiation of anti-IL5(R) in real life and in RCTs.

Materials 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-centred (SHARP Central) registry. We compared the baseline characteristics of the patients starting anti-IL5(R) from 11 European countries within SHARP with the baseline characteristics of the severe asthma patients from 10 RCTs (four for mepolizumab, three for benralizumab and three for reslizumab). Patients were evaluated following eligibility criteria from the RCTs of anti-IL5 therapies.

Results Patients starting anti-IL5(R) in Europe (n=1231) differed in terms of smoking history, clinical characteristics and medication use. The characteristics of severe asthma patients in the SHARP registry differed from the characteristics of patients in RCTs. Only 327 (26.56%) patients 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: ⩾10 pack-years, respiratory diseases other than asthma, Asthma Control Questionnaire score ⩽1.5 and low-dose inhaled corticosteroids.

Conclusion A large proportion of patients in the SHARP registry would not have been eligible for anti-IL5(R) treatment in RCTs, demonstrating the importance of real-life cohorts in describing the efficacy of biologics in a broader population of patients with severe asthma.

Introduction

Asthma is a common chronic disease affecting ∼5–10% 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/IL5(R) 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 randomised controlled trials (RCTs) conducted for regulatory purposes [3].

In clinical practice, however, it has been demonstrated that only 25–35% of severe asthma patients who use biologics 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 biologics for severe asthma set by the European Medicine Agency (EMA) are also very broad. Roughly, the anti-IL-5/IL5(R) 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-IL5 biologics 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 organisation of the healthcare 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-IL5(R) in real life and in RCTs as judged by different inclusion and exclusion criteria.

We hypothesised 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-IL5 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-IL5 biologics (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 biologics 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 from difficult to treat asthma as stated in the national guidelines [1]. All patients 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); www.castoredc.com/electronic-data-capture-system) in a standardised 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 an oral corticosteroids (OCS) course of at least 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 1 January 2016 and 24 September 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 [9–18] (supplementary figure S1). 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 or more of the inclusion criteria stated in RCTs of the patient prescribed one of the biologics.

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 summarised using proportions and mean$\pm_{SD}$.

For the second aim, data from the SHARP registry were compared with data derived from RCTs using the Welch-modified t-test for continuous and χ^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 means 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 analysed data from SHARP Central Registry of 1231 severe asthma patients that initiated anti-IL5 treatments such as benralizumab, mepolizumab or reslizumab. For the analysis, 11 countries were analysed: 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-IL5(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.

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

	HR	HU	LT	LV	NL	PL	RO	RS	SE	SI	TR
Patients n	106	48	60	15	814	17	21	45	20	43	42
Age years	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 years	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
Sex, 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[#]	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 kg·m^{-2}	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)
FEV_1 preBD L	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	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
FEV_1 preBD %	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 %	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
FEV_1/FVC preBD %	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
FEV_1 postBD L	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	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
FEV_1 postBD %	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 %	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
FEV_1/FVC postBD %	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 cells·µL^{-1}	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 cells·µL^{-1}	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^{-1}	194.0±449.34	134.5±768.90	84.7±206.68	197.9 ±2678.21	144.4±537.04	445.2±1059.14	453.6±552.24	136.8±238.93	160.0552.55	267.0±156.41	187.0±323.40
F_{ENO} ppb	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	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	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	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)
>5 per year	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 µg·day^{-1}	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	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	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	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)

Data are presented as n (%) or mean±SD unless indicated otherwise. 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; FEV_1: forced expiratory volume in 1 s; preBD: prebronchodilator; postBD: postbronchodilator; NaN (NA): not available; FVC: forced vital capacity; IgE: immunoglobulin E; F_{ENO}: fraction exhaled nitric oxide; OCS: oral corticosteroids; ACQ: Asthma Control Questionnaire; ICS: inhaled corticosteroids; LABA: long-acting β-agonists; LAMA: long-acting muscarinic antagonists; LTRA: leukotriene receptor antagonists. [#]: pack-years was calculated excluding nonsmokers (pack-years=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 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 nonsmokers and ex-smokers (SE: 50% nonsmokers and 50% ex-smokers; NL: 53.6% nonsmokers and 45.6% ex-smokers).

Most countries reported that patients had experienced between two and five 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 OCS. Long-acting muscarinic antagonists (LAMA) and leukotriene receptor antagonists (LTRA) were variably prescribed among countries.

The cohort was further characterised by comorbidities that are known to be associated with asthma. The frequencies of the comorbidities were variable between countries (table 2), the most frequent being: allergic rhinoconjunctivitis (the highest percentage registered in Poland 52.9%) chronic rhinosinusitis (the highest percentage reported in Hungary of 89.6% and in Croatia with 73.6%), nasal polyps (Hungary and Latvia reported the highest percentage of 62.5% and 53.3%, respectively) and gastro-oesophageal reflux disease (GERD) mostly reported in Hungary (56.2%).

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

All three biologics were prescribed among the 10 countries, with mepolizumab being the most prescribed, and reslizumab the least (table 3), with the exception of Romania and Serbia where benralizumab was most prescribed (100% and 84.4%, respectively).

An overview of the number and the percentage missing data per variable is provided in supplementary 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 summarised 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 RCT studies were selected: four for mepolizumab [15–18], three for benralizumab [12–14] and three for reslizumab [9–11]. An overview of trials' eligibility criteria extracted from the study protocols is provided in supplementary table S2. A summary of the results of the comparison between the trial population and the SHARP Central population anti-IL5(R) starters is provided in supplementary tables S3 to S5. Furthermore, an additional comparison of the characteristics of the eligible patients per biologic with the respective RCTs is presented in supplementary tables S3.1, S4.1 and 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

TABLE 2 Summary of comorbidities in patients with severe asthma included in SHARP Central

	HR	HU	LT	LV	NL	PL	RO	RS	SE	SI
Patients n	106	48	60	15	814	17	21	45	20	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 rhinoconjunctivitis	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)
Gastro-oesophageal 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)

Data are presented as n (%). Turkish data were not included because of the absence of information available at that time on comorbidities. HR: Croatia; HU: Hungary; LT: Lithuania; LV: Latvia; NL: Netherlands; PL: Poland; RO: Romania; RS: Serbia; SE: Sweden; SI: Slovenia; OSAS: obstructive sleep apnoea syndrome.

TABLE 3 Prescription of anti-interleukin (IL)5(R) per country

	Mepolizumab	Reslizumab	Benralizumab
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)

Data are presented as n (%). Countries with information for <five patients are reported "<5" for privacy. HR: Croatia; HU: Hungary; LT: Lithuania; LV: Latvia; NL: Netherlands; PL: Poland; RO: Romania; RS: Serbia; SE: Sweden; SI: Slovenia; TR: Turkey. [#]: lack of data based on the fact that SI at that time was still building the registry.

demographic (*e.g.* age and sex) and clinical characteristics (*e.g.* inhalers usage and OCS 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 patients, 991 (80.5%) did not fulfill 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 to inclusion and exclusion criteria with respect to the criteria were: high inhaled corticosteroid (ICS) dosage, ACQ score ⩾1.5, pack-years ⩾10, better lung function and the presence of other respiratory or eosinophilic conditions, as 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 supplementary figure S2; RCT-eligible patients in SHARP Central reported to have more frequent comorbidities such as chronic rhinosinusitis, nasal polyps and allergic rhinoconjunctivitis.

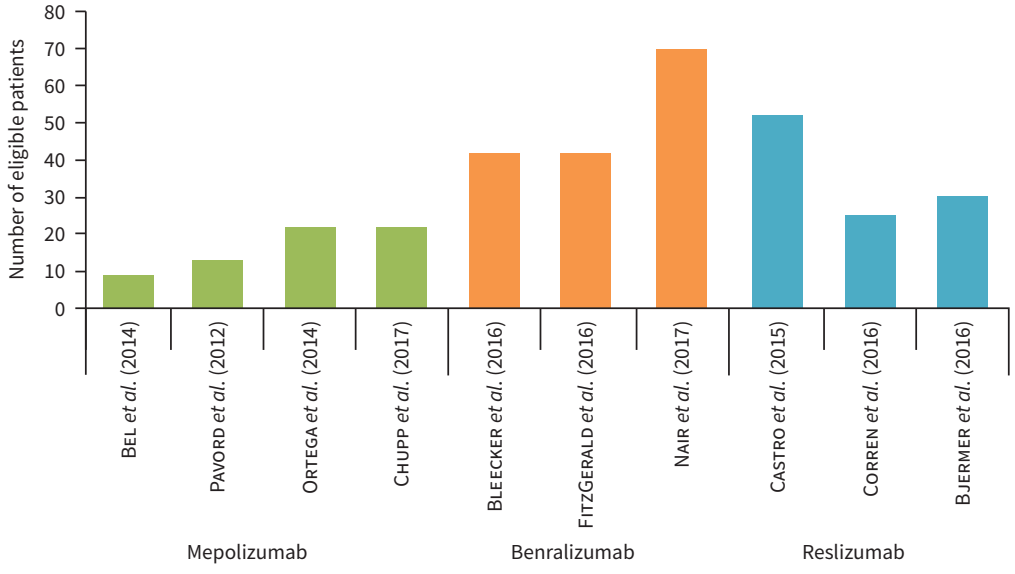

FIGURE 1 Distribution of the eligibility per trial for severe asthma patients in SHARP following inclusion/exclusion criteria of the selected trials.

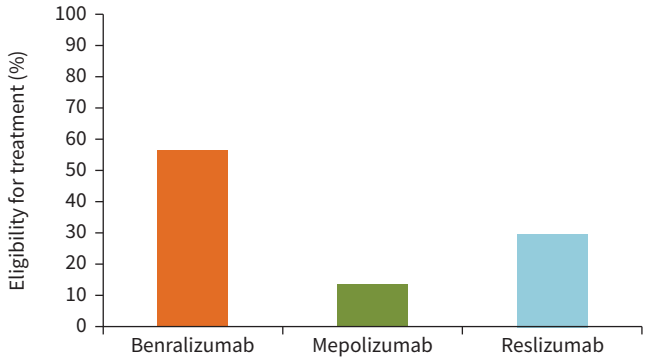

FIGURE 2 Treatment eligibility stratifying per biologic therapy.

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 Netherlands (58.7%) and highest in Romania (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 (79.6%). The reported other respiratory diseases were: bronchiectasis (the highest number of patients registered in Romania (61.9%)) and eosinophilic granulomatosis with polyangiitis (EGPA) mainly reported in Croatia (17.7%) as well as eosinophilic pneumonia with 13.5% and 17.1% of the patients reporting allergic bronchopulmonary aspergillosis, mostly in Sweden (6.2%). Five countries reported RCT-ineligible severe asthma patients according to Asthma Control score ⩽1.5: Croatia mean±SD 1.12±1.15, Hungary 1.12±0.66, Poland 1.45±0.82, Sweden 1(NA) and Turkey 1.33(NA). In all countries the RCT-ineligible patients received a lower dose of ICS compared to trials, with the lowest dose registered in Latvia (mean±SD 314.5±230.8 µg·day^{-1}).

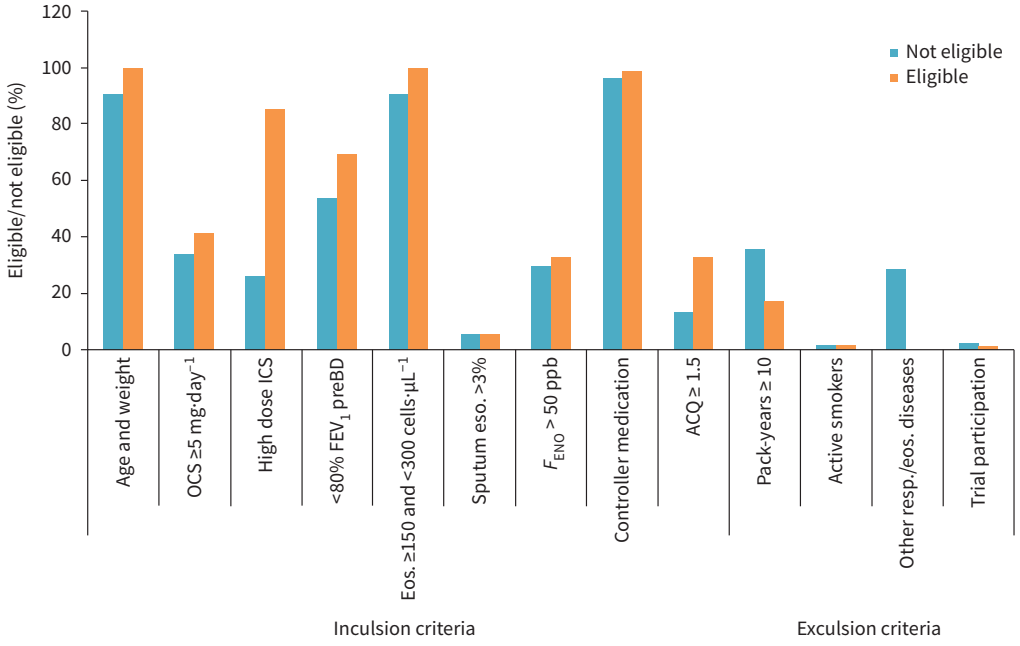

FIGURE 3 Overall distribution of the severe asthma SHARP patients according to trials' eligibility. Trial ineligibility was defined as: fulfilling at least one of the exclusion criteria stated in the selected randomised controlled trials (RCTs); or not fulfilling one or more of the inclusion criteria stated in RCTs of the patient prescribed one of the biologics. OCS: oral corticosteroids; ICS: inhaled corticosteroids; FEV_1: forced expiratory volume in 1 s; preBD: prebronchodilator; eos.: eosinophils; F_{ENO}: exhaled nitric oxide fraction; ACQ: Asthma Control Questionnaire; resp.: respiratory.

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TABLE 4 Characteristics of patients with severe asthma included in SHARP Central, ineligible for Phase III randomised controlled trials

	HR	HU	LT	LV	NL	PL	RO	RS	SE	SI	TR
Patients 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-smoker	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-smoker	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 smoker	4 (4.2)	3 (7.3)	4 (8.2)	0	6 (0.9)	0	0	0	0	0	1 (2.4)
Pack-years	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	11 (11.4)	3 (7)	11 (22)	2 (14)	132 (21)	2 (15)	13 (61.9)	13 (32)	1 (6)	2 (5)	NA
EGPA	17 (17.7)	0	2 (4)	1 (7)	36 (5)	0	2 (9)	0	2 (12)	1 (2)	NA
Eosinophilic pneumonia	13 (13.5)	3 (7)	0	2 (14)	50 (8)	2 (15)	1 (4)	0	0	2 (5.3)	NA
ABPA	4 (4.2)	0	0	0	14 (2)	0	1 (4.7)	0	1 (6.2)	0	NA
ACQ 5	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)	NA	1 (NA)	2 (NA)	1.33 (NA)
ICS dose µg·day^{-1}	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

Data are presented as n (%) or mean±SD. HR: Croatia; HU: Hungary; LT: Lithuania; LV: Latvia; NL: Netherlands; PL: Poland; RO: Romania; RS: Serbia; SE: Sweden; SI: Slovenia; TR: Turkey; EGPA: eosinophilic granulomatosis with polyangiitis; ABPA: allergic bronchopulmonary aspergillosis; ACQ: Asthma Control Questionnaire; ICS: inhaled corticosteroids; NA: not available.

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-IL5(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-IL5(R) treatment if the inclusion and exclusion criteria of the RCTs had been followed.

The present study confirms and extends the results from a recent study by Richards *et al.* [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 (HES) or fixed airway obstruction.

Trial eligibility in a real-life severe asthma cohort was also assessed by Brown *et al.* [19] who selected data from the Wessex Severe Asthma Cohort and compared these with 37 RCTs evaluating 20 biological therapies. They found that only 9.8% (range 3.5% to 17.5%) of patients would have been eligible for inclusion in trials investigating anti-IL5 treatment. In line with our results, 26% of severely asthmatic patients in their study were current smokers or ex-smokers with a smoking history of $\geqslant$10 pack-years and were considered ineligible for RCTs even if they reported high blood or sputum eosinophil counts.

Another study [20] 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-IL5(Rα) 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 [21] showed that mepolizumab improved symptom control (Asthma Control Test score from a mean±SD of 13±4.8 to 20.7±4.6) and reduced asthma exacerbation and OCS use in patients with coexistent severe asthma and bronchiectasis after 6 months of treatment.

Also patients with EGPA and HES have been shown to benefit from anti-IL5 treatments. Two studies reported relevant steroid-sparing effect of reslizumab and benralizumab for severe asthma patients with EGPA [22, 23], and a double-blind phase III RCT of 136 participants reported in addition an improvement in the disease remission with mepolizumab at the dosage of 300 mg [24]. In fact, the EMA have 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 Food and Drug Administration (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 exert at the same time a significant steroid-sparing effect in patients with persisting severe eosinophilic asthma after systemic disease resolution [25–27]. 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 [28] 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-IL5(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 [29], 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 of anti-IL5(Rα) RCTs, showing that age does not negatively affect the efficacy of these monoclonal antibodies. Thus, the use of these biologics could also be extended to a frail

population [30, 31]. The same findings were recently confirmed by a real-life analysis focusing on clinical response of mepolizumab and omalizumab in different sexes and age ranges [32].

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-IL5 treatment. Not only patients with multiple comorbidities, whether or not related to asthma, but also the elderly, heavy smokers and patients with airway remodelling appear to benefit from this treatment. Second, our study emphasises 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 efficacy of this biological therapy. Third, our study highlights the importance of harmonising 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 ongoing 3TR pan-European consortium [33, 34]. Like SHARP Central, these multinational programmes will hopefully contribute to a better characterisation 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 characterise patients with severe asthma who were prescribed anti-IL5(Rα) 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 harmonisation. Potential limitations of this study include first that our results represent a snapshot, which may change over time, since collection of data in the SHARP Central Registry is still ongoing. Yet, we were able to select >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 body mass index, but not in qualitative data like smoking history or comorbidities. Lastly, we could not include the same information per trial when we compared baseline characteristics of SHARP Central Registry 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 Registry might have been retrieved in a different way to that in RCTs (*e.g.* exacerbations previously explained). Therefore, we could only present comparison of data that we were sure could have been retrieved in the same way to that in the SHARP central registry. Even though this information might be considered incomplete, it is an important "first-step" to understand the discrepancies in real-life populations with RCTs.

In conclusion, we have demonstrated that patients receiving asthma biologics in routine clinical asthma care, across a wide European spectrum, differ from patients who participate 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 randomised trials might derive genuine benefits from anti-IL5 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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