Characteristics and treatment regimens across ERS

SHARP severe asthma registries

Job J.M.H. van Bragt1, Ian M. Adcock2, Elisabeth H.D. Bell, Gert-Jan Braunstahl3, Anneke
Ten Brinke4, John Busby5, Giorgio W. Canonica6, Hui Cao7, Kian Fan Chung8, Zsuzsanna
Csoma9, Barbro Dahlén10, Elizabeth Davin11, Susanne Hansen12, Enrico Heffler6, Ildiko
Horvath6, Stephanie Korn13, Maxim Kots14, Piotr Kuna15, Namhee Kwon16, Renaud Louis17,
Vicente Plaza18, Celeste Porsbjerg19, David Ramos-Barbon18, Levi B. Richards1, Sabina
Skrgat20, Jacob K. Sont21, Susanne J.H. Vijverberg1, Els J. Weersink1, Valentyna Yasinska10,
Scott S. Wagers22, Ratko Djukanovic23, Anke H. Maitland-van der Zee1, on behalf of the
SHARP CRC24.

1Amsterdam UMC, University of Amsterdam, Department of Respiratory Medicine,
Amsterdam, The Netherlands
2National Heart and Lung Institute, Imperial College London, London, United Kingdom
3Franciscus Gasthuis & Vlietland, Rotterdam, The Netherlands
4Medical Centre Leeuwarden, Leeuwarden, The Netherlands
5Centre for Public Health, School of Medicine, Dentistry and Biomedical Sciences, Queen’s
University Belfast, Belfast, United Kingdom
6Personalized Medicine Clinic, Asthma and Allergy, Humanitas Clinical and Research
Center, Humanitas University, Rozzano and SANI-Severe Asthma Network Italy, Milan, Italy
7Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA
8Airway Disease, National Heart and Lung Institute, Imperial College London, London,
United Kingdom
9National Koranyi Institute of Pulmonology, Budapest, Hungary
10Division of Respiratory Medicine and Allergy, Department of Medicine, Karolinska
University Hospital, Huddinge, Sweden
11 European Lung Foundation, Sheffield, United Kingdom

12 Center for Clinical Research and Disease Prevention, Bispebjerg and Frederiksberg Hospital, The Capital Region, Copenhagen, Denmark

13 Universitätsmedizin Mainz, Mainz, Germany

14 Chiesi Farmaceutici, Global Clinical Development, Parma, Italy

15 Department of Internal Medicine, Asthma and Allergy, Medical University of Lodz, Lodz, Poland

16 Respiratory Medical Franchise, GSK, Brentford, United Kingdom

17 Department of Pulmonary Medicine, Centre Hospitalier Universitaire (CHU), GIGA\textsuperscript{3} Research Group, Liege University, Liege, Belgium

18 Respiratory Medicine Department & Biomedical Research Institute, Hospital de la Santa Creu i Sant Pau, Universitat Autònoma de Barcelona, Barcelona, Spain

19 Respiratory Research Unit, Department of Respiratory Medicine, Bispebjerg University Hospital, Copenhagen, Denmark

20 University Clinic of Respiratory and Allergic Diseases, Golnik, Slovenia

21 Department of Biomedical Data Sciences, section Medical Decision Making, Leiden University Medical Center, Leiden, The Netherlands

22 BioSciConsulting, Maasmechelen, Belgium

23 NIHR Southampton Respiratory Biomedical Research Unit, Faculty of Medicine, University of Southampton, Southampton, United Kingdom

24 Members of the SHARP CRC are mentioned in the acknowledgements section
Corresponding author: Job J.M.H. van Bragt
Amsterdam UMC, location AMC
Department of Respiratory Medicine, room F5-260
Meibergdreef 9
1105 AZ, Amsterdam
The Netherlands
T: +31-(0)20-5661660 | E: j.j.vanbragt@amsterdamumc.nl

Take home message
The severe asthma population in Europe is heterogeneous and differs in clinical characteristics and treatment. Harmonisation across registries and guidelines is needed and requires collection of same data across cohorts to enable future research in SHARP.

Plain Language Summary
What is it about?
Severe asthma is a very serious condition with a large impact on the life of patients. Researchers from different countries in Europe have systematically collected data from severe asthma patients in registries. This study was set up to provide an overview of what data is currently collected in those registries and to show what differences exist between patients with severe asthma in different countries in Europe. We found that many differences exist between the characteristics of patients in different European countries. We also found that treatment of patients with severe asthma is different across European countries.

Why is it important?
Much is still unknown about severe asthma and it seems to be a very complex disease. The current study can help to provide a view on what is considered severe asthma in different countries in Europe. This is important to provide new insights in what is necessary for doing research in a large scale registry across European countries and, in addition, to make sure that registries across Europe use the same standards and definitions.
Abstract

Little is known about the characteristics and treatments of patients with severe asthma across Europe but both are likely to vary. This is the first study in the ERS Severe Heterogeneous Asthma Research collaboration, Patient-centred (SHARP) and it is designed to explore these variations. Therefore, we aimed to compare characteristics of patients in European severe asthma registries and treatments before starting biologicals. This was a cross-sectional retrospective analysis of aggregated data from 11 national severe asthma registries that joined SHARP with established patient databases. Analysis of data from 3,233 patients showed many differences in characteristics and lifestyle factors. Current smokers ranged from 0% (Poland, PL, Sweden, SE) to 9.5% (Belgium, BE), mean BMI ranged from 26.2 (Italy) to 30.6 kg/m2 (UK) and the largest difference in mean pre-bronchodilator FEV1% pred. was 20.9% (Netherlands vs Hungary). Before starting biologicals patients were treated differently between countries: mean ICS dose ranged from 700-1335 µg/day between those from Slovenia (SL) vs PL when starting anti-IL-5 antibody and from 772-1344 µg/day in those starting anti-IgE (SL vs Spain). Maintenance OCS use ranged from 21.0% (BE) – 63.0% (SE) and from 9.1% (Denmark) to 56.1% (UK) in patients starting anti-IL-5 and anti-IgE, respectively. The severe asthmatic population in Europe is heterogeneous and differs in both clinical characteristics and treatment, often appearing not to comply with the current ERS/ATS guidelines definition of severe asthma. Treatment regimens before starting biologicals were different from inclusion criteria in clinical trials and varied between countries.
Introduction

The Severe Heterogeneous Asthma Research collaboration, Patient-centred (SHARP) was set up in 2018 to harmonise severe asthma management across Europe and unravel underlying heterogeneity in a patient-centred way [1]. The current project involves the first structured assessment and comparison of national severe asthma registries that are part of SHARP to discover strengths/weaknesses in those registries and to evaluate severe asthma and its treatment across Europe.

Significant progress has been made in the field of severe asthma since the turn of the millennium [2]. Especially, the introduction of novel biologicals for patients with severe asthma, has provided new effective options for medical treatment, beginning with the anti-IgE monoclonal antibody, omalizumab, and more recently anti-IL-5 antibodies, mepolizumab, reslizumab and benralizumab. The use of these biologicals is often restricted to patients who fulfil the definition of severe asthma according to ERS/ATS guidelines in whom all potential aggravating factors have been eliminated and pre-specified criteria fulfilled, such as high dose ICS/LABA treatment, multiple exacerbations in the previous year and/or chronic use of oral glucocorticoids [3].

The most recent GINA difficult-to-treat and severe asthma guide introduces a new approach to the management of asthma [4], better reflecting the recommendations of the Lancet commission on asthma [5, 6] that highlighted the need for a multidimensional assessment and the introduction of treatable mechanisms in asthma management. However, the definition of severe asthma is still not unambiguous and it has been suggested that an improved definition, including risk assessment and a better reflection of clinical reality, should be established. Asthma death is arguably the most severe outcome, but most deaths occur in patients with non-severe asthma with low levels of treatment [7]. Many disease aggravating factors, both patient related (e.g. psychological factors, co-morbidities) and environmental, (airborne allergens, air pollution), socio-economic (housing, health insurance)
and health care accessibility factors, are difficult or impossible to eliminate. Furthermore, the expertise of the treating physician and the facilities of the treatment centre are likely to influence levels of asthma control. Finally, the choices of treatment (including starting biologicals) are effected by differences in health care systems, reimbursement policies and accessibility to medication.

In the present study, we explored the prevalence as well as the characteristics of patients with “severe asthma” reported by physicians, which are likely to differ depending on the region, climate, health care system and expertise of the treatment team. Furthermore, we explored the severity of disease (using the treatment of the patient and biomarkers as a proxy) of severe asthma patients before starting biologicals, also expecting differences between European countries. We compared the characteristics of those patients who started with high-cost therapies (biologicals, bronchial thermoplasty, high altitude revalidation) within these registries, and stratified the patient cohort for the two most commonly used groups of biologicals (anti-IL5 and anti-IgE). This study showed the need for harmonisation across registries and guidelines and the requirement to collect a same set of minimal clinical data across cohorts which will enable better co-ordination of treatment efforts using biologicals across Europe.

**Materials and methods**

*Study subjects*

Data from 11 different European national registries for severe asthma (figure 1) were eligible for inclusion in the analysis. There were no general inclusion criteria provided for the patients in these registries, so these differed between registries (figure 2). Most European registries included patients who fulfilled the severe asthma criteria according to the joint ERS/ATS guidelines [3], but in some cases national asthma guidelines were used or all patients who attended specialist asthma centres were qualified for inclusion. Four registries focused enrolment into registries of patients that were either in the process of being considered for or
were starting treatment with biologicals. One registry selected only patients with a smoking history <5 pack-years and one registry included all patients who attended specialist referral centres for severe asthma.

**Study design**

This study was a cross-sectional, retrospective analysis of aggregated registry data. In view of the restrictions imposed on data confidentiality before and, in some cases, after imposition in the European Union of the General Data Protection Regulation (GDPR), data were received from individual national registries in aggregate form composed of counts (with percentages) mean ± standard deviation (SD) and median with interquartile range (IQR, Q1-Q3).

**Analysis**

A descriptive comparison was performed for the clinical characteristics in the different registries. To describe differences in treatment regimens and biomarkers, comparisons were made prior to starting high-cost therapies. For those patients who had already discontinued these therapies, and where information before start was not available, data from more than 6 months after stopping of high-cost therapies was used. High-cost therapies were defined as treatments with biologicals, bronchial thermoplasty or high-altitude treatment.

**Results**

Data from a total of 3,233 patients classified as having severe asthma by the 11 different European registries were used for the analysis. Table 1 indicates the abbreviations that are used to identify the different countries. The registries varied in size (Sweden, SE; n= 27 – UK; n=765). The characteristics of the different populations are shown in table 2. None of the participating registries collected the full set of variables requested. Data that were not collected or not available in a registry are shown in the different tables.
**Differences in baseline clinical characteristics.**

The mean age of patients ranged from 44.4 (Germany, DE) to 58.3 years (Hungary, HU). The percentage of males ranged from 30% (Slovenia, SL) to 51.9% (SE). Current smokers ranged from 0% (Poland, PL and SE) - 9.5% (Belgium, BE). The percentage of ex-smokers varied from 10.8% (HU) to 41.3% (The Netherlands, NL); in Hungary, only patients with a smoking history of <5 pack-years were enrolled into the registry. Half of the registries predominantly included patients with adult-onset severe asthma (NL, UK, HU, SE, Denmark, DM, and SL), while four registries consisted mainly of patients with childhood-onset asthma (BE, Italy, IT, PL and DE). Based on mean FEV₁ and FVC (% of predicted), patients in the Dutch registry had the best lung function, while those in the Hungarian had the worst lung functions (FEV₁: 76.9% vs. 56.0% and FVC: 98.3% vs. 76.6%). Median blood eosinophil levels varied from $0.230 \times 10^9$ cells/ml (NL) to $0.800 \times 10^9$ cells/ml (SE), median serum total IgE varied from 144 IU/ml (NL) to 275 IU/ml (SE) and median FeNO varied from 25 ppb (BE) to 66 ppb (SL). Between 54.6% (IT) and 100% (HU, SE) of the patients were uncontrolled as judged from patient-reported questionnaire scores (ACQ or ACT).

Most registries enrolled patients being treated in a tertiary care centre; however, a small
group of patients was included in primary care (ES) and four registries (ES, NL, BE and HU)
included up to 33.8% in secondary care hospitals. In most registries >90% of the patients
were treated according to GINA step 4 or 5 guidelines [7]; in DM this was 77.6% (evaluated
before patients started biologicals) and in 6 registries (HU, PL, SE, DE, IT, SL) 100% of
patients were at step 4 or 5. The percentage of patients on biologicals ranged from 0% (SE)
to 71.0% (PL). The most frequently given biological in 7 registries was anti-IgE (BE, ES, HU,
PL, SE, DE, IT, SL), and in 3 registries it was anti-IL5 (NL, UK, DM). The registries in NL, BE
and SL enrolled patients who had undergone bronchial thermoplasty and the registry in NL
also included patients who had received high-altitude treatment (14%). The mean ICS dose
(fluticasone equivalent dose) ranged from 491±163 µg/day (SL) to 1225±445 µg/day (ES).
The maintenance OCS median dose ranged from 7.5 mg/day (HU) to 10.7 mg/day (IT).
Treatment regimens of patients starting high cost therapies

Table 3 shows medication data of 1,962 patients included in the registries prior to starting or >6 months after stopping high cost therapies. In 6 registries (BE, ES, HU, SE, SL, DM), most patients were not treated according to GINA treatment step 5. Short-acting β-agonists were the most used reliever medications in all but one registry (ES) where the most frequent relievers were short-acting muscarinic antagonist (SAMA). SABA and/or SAMA use varied between 4.0% (IT) to 100% (HU, PL, SE). Long-acting beta-agonist (LABA) use varied from 80.3% (PL) to 100% (IT, HU and SE). Long-acting muscarinic antagonists (LAMA) were used in all countries and varied from 14.0% (HU) to 56.8% (UK). In 7 registries (ES, HU, PL, SE, IT, SL, UK) all patients were on ICS, while in NL, BE and DM this was 99.3%, 97.0% and 93.9% respectively. Mean fluticasone equivalent doses ranged from 1320±465 µg/day (ES) to 570±497 µg/day (IT).

Figures 3 and 4 provide an overview of maintenance therapy for severe asthma patients before starting with anti-IL5 biologicals (mepolizumab, reslizumab or benralizumab; n=577) and anti-IgE biologicals (omalizumab; n=553). In most of the registries, all patients were on ICS before starting anti-IL5 (in DM this was only 94.7%), although there were differences in ICS-dose, ranging from 1335±529 (PL) to 700±118 µg/day (SL). Information on treatment before starting omalizumab was available in 6 registries. ICS use was less than 100% in BE (96.6%) and DM (90.9%) and the mean dose ranged from 1344±540 (ES) to 772±191 µg/day (SL). In four registries, all patients were using LABA before starting anti-IL5 (ES, HU, SE, SL), while in other countries this ranged from 25.0% (PL) to 94.4% (NL). LAMA use in anti-IL5 starting patients varied between 0% (HU) and 79.1% (SL). LAMA use in anti-IgE starting ranged from 12.5% (HU) – 100% (SL). OCS was used as a maintenance therapy before starting with anti-IL5 in all registries and ranged from 21.0% (BE) – 63.0% (SE) of the population. Before starting anti-IgE, OCS was also used in all registries, varying between 9.1% (DM) and 56.1% (UK) of the population.
Table 4 shows differences between registries in biomarkers before starting treatment with biologicals. Median blood eosinophil levels before starting anti-IL5 therapy were higher than levels seen before starting anti-IgE treatment in all registries. The levels of median blood eosinophils before starting anti-IL5 treatment ranged from $0.270 \times 10^9$ cells/L (DM) to $0.800 \times 10^9$ cells/L (SE). The median concentrations of serum total IgE before start with anti-IgE treatment ranged between 118 IU/ml (SL) to 324 IU/ml (UK).

Discussion

This first collaborative study in the SHARP consortium has made several important observations. Across Europe there are large differences in characteristics and lifestyle factors of patients with severe asthma. Treatment regimens and biomarkers in patients starting biologicals and criteria for their prescription also seem to differ between countries. The patients included in the various countries of Europe for treatment with biologic therapies, who we would consider to suffer from severe asthma, did not fit the criteria of the definition of severe asthma as defined by ERS/ATS and GINA, and they also did not meet the criteria used to recruit patients in the Phase 3 trials of these biologic therapies. The reasons for these differences are as yet unclear and will need to be addressed as the SHARP CRC moves to harmonize the data that are collected in the different national registries.

Differences between registries

The data in this study clearly shows large variation in the baseline characteristics of asthmatics enrolled in the 11 European registries. This could be due to differences in the definition of severe asthma across the different registries. The disparities could, in principle, also reflect differences in overall severity of the broader asthma population in each country, however our data do not allow us to explore to what extent the enrolled patients reflect the general asthma population. Lung function results, expressed as pre-BD FEV1 and FVC (% of predicted), were in both cases highest in NL and lowest in HU, with differences as high as
20.9% and 21.7%, respectively. We do not presently know what causes these differences; patients in the two registries were on similar treatment, and FENO levels and blood eosinophil counts were not different. However, possible explanations may be in differences in life-time dose or onset of therapy with ICS, which would result in progressive loss of lung function, or in the difference in OCS use between HU and NL (60% vs. 26% before high-cost therapies) and the resulting effects on blood eosinophils and FeNO. Important differences were also found in the percentage of adult onset asthma patients (64.9%), a clinical phenotype of asthma that is known to be more severe than early-onset asthma [8]. Furthermore, the percentages of patients with uncontrolled asthma based on questionnaire scores (45.4 % difference) and asthma-related hospitalization during the past 12 months (43.5% difference) point to possible differences in the quality of care (e.g. access to specialist care). Other potential explanations might be exposure to asthma triggers like outdoor and/or indoor pollution (including cigarette smoke) that may have resulted in worsening lung function. Whilst these factors could not be assessed in the current analysis because relevant data were not collected, they could be the subject of future studies by the SHARP CRC.

Smoking patients, or smokers with a history ≥10 pack-years are almost never included in asthma trials due to the risk of confounding effects of smoking and the undesired inclusion of COPD patients. In real life, however, significant proportions of severe asthma patients also smoke, with rates in excess of 4% found in BE, UK, ES and HU. Again, differences between registries from different countries were large, up to 30.7 %-points for the percentage of never-smokers, with differences in median pack-years of >14 years. Interestingly, differences in smoking do not necessarily reflect the differences in lung function; the Netherlands included more ex-smokers and median pack-years is higher than in Hungary despite patients in Hungary having worse lung functions. In general, BMI appeared to be less variable. Nevertheless, the largest difference here was 4.4 kg/m² and the difference in
average BMI between the UK (30.6 kg/m²) and Italy (26.2 kg/m²) suggests that obesity in severe asthma patients may be a significant problem in the UK, but not in Italy.

Treatment of patients starting on high-cost therapies

The differences in OCS use before starting high-cost therapies between registries from different countries was striking. The percentage of patients on maintenance OCS varied greatly (largest difference: 61.6 %-point between IT and ES), suggesting very different prescribing regimens across Europe. When specifically studying patients starting anti-IL5 and omalizumab, large differences in treatment regimens were also found. OCS use in those starting anti-IL5 treatment were highest in the UK and differed most from the clinical practice in Belgium (52.2% difference). As expected, all patients starting anti-IL5 biologicals were using regular ICS, although there was marked variation in the daily dose, with fluticasone equivalent differences of up to 635 µg/day (PL vs SL). Why this is the case is unclear. Potential explanations, which will require focused study by the SHARP CRC, include cost of treatment and fear of high-dose treatment related side-effects.

Patients starting omalizumab showed similar differences between registries, with largest differences in OCS use and mean dose between the UK and Belgium (45.1 %-points and 10.0 mg/day respectively). All patients starting omalizumab were on ICS except for Belgium, and the largest fluticasone equivalent difference was 571 µg/day (ES vs SL). LAMA can be used as step-up treatment after GINA step 4 [9] and the results show that the percentage of patients on LAMA in both anti-IL5 and anti-IgE varied significantly. LAMA use was common in Slovenia, although this observation was based on a small sample size (24 starting ant-IL5 antibody and 9 starting Omalizumab). Of note, LAMA were hardly used in Hungary, Poland and Spain. Taken together, these differences in treatment suggest a difference in criteria applied (not necessarily required) to prescribe anti-IL5 and anti-IgE biologicals.

Deviations from guidelines and trial criteria
An important issue that this study highlights is that criteria on which severe asthma is defined currently by international guidelines and those used in clinical trials with biologicals do not match clinical reality. For example, not all patients enrolled in the registries are on GINA step 4/5 treatment and ICS doses in patients starting with biologicals do not always correspond to those applied as inclusion criteria in trials and in the joint ERS/ATS criteria. Fluticasone equivalence of >1000µg/day (ex-actuator; 880µg/day) was an inclusion criterion for mepolizumab trials [10, 11] and doses >1000µg/day are considered high-dose according to the ERS/ATS guidelines [3]. In this study, patients in several registries (BE, UK, ES, HU, SL) were on mean doses <1000µg/day, suggesting that a significant proportion of patients in the registries would not meet the mepolizumab trial inclusion criteria or do not meet the international ERS/ATS criteria for severe asthma. This deviation in ICS dose can be potentially explained by different interpretations between what is considered high dose ICS by the ERS/ATS and GINA (>500µg/day fluticasone equivalents). Additionally, for the BE registry, these data can be partially explained by to the inclusion of a large number (roughly 25-30%) of non-T2 asthma patients, who may be less responsive to ICS. A similar picture arises with anti-IgE treatment. Mean fluticasone equivalent ICS doses before starting omalizumab were <1000µg per day in Belgium, the UK and Slovenia; thus, at least part of the population does not have severe asthma according to international ERS/ATS guidelines.

The first clear message that arises is the need for agreement between ERS/ATS guidelines and GINA, as the current differences in definitions are a cause for confusion among pulmonary physicians. One of the possible explanations of the differences between the characteristics of patients included in the severe asthma registries and the characteristics that were expected according to ERS/ATS guideline definition of severe asthma might suggest that some patients do not fulfil guideline criteria but are being considered as having severe asthma by clinical severe asthma experts. These differences will require more analysis, including the processes whereby biologics are offered to patients. In the UK, the main criteria required by the National Institute of Clinical Excellence for both omalizumab
and anti-IL5 biologicals is the frequency of exacerbations (three – four) in the previous 12 months or maintenance OCS [12–14], and these are implemented rigorously by the commissioning groups that regulate the use of biologicals. One plausible explanation for the observation in the UK is that the frequency of exacerbations is not used to define asthma severity. Furthermore, patients treated with biologicals in clinical practice do not always fulfil the criteria that were used for inclusion in the biological trials. Although this study was not designed to evaluate the efficacy of biological therapies, this suggests a need for observational studies targeting the efficacy of biologicals in patients who were not enrolled in trials that resulted in their approval. Such observational studies would provide more insight in the efficacy of biologicals in daily practice; however, the differences in countries as described here should be considered.

*European harmonisation*

The previous issues raise awareness that severe asthma research needs to consider more the complexity and heterogeneity between different populations of chronic respiratory diseases. New discoveries will need large amounts of data that can only be collected in international consortia, therefore there is an urgent need to harmonize datasets on severe asthma across Europe. An international consensus needs to be reached on a minimal set of variables that should be collected in the national registries that take part in SHARP. When studying lung function, for example, all registries currently include information on pre-bronchodilator (BD) FEV₁, but only 9 out of 11 registries also record pre-BD FVC. Information on lung function reversibility is even less common, with post-BD FEV₁ currently recorded in only 7 registries. The bigger challenge, however, lies in the harmonization of definitions of variables. The definition for FEV₁ and FVC is rather simple, whilst it is not straightforward for adherence to therapy. Countries retrieved these data in different ways; by checking prescription records, check-up by a dedicated asthma nurse, by doctor’s assessment or checking a database whether a patient was registered as showing ‘good compliance’. Accordance on a minimal set of well-defined key variables is needed to
increase the usability of the SHARP platform and should be subject of future studies. The data collected in this study should be a stepping-stone to start the discussion about more standardized practice for severe asthma care in Europe.

Earlier research

Several of the participating registries have already published analyses of their data [15–17]. The heterogeneity found in this study is in line with the analyses of registries in Belgium, Italy and the UK, where differences in inflammatory characteristics [15] amongst patient populations were found even between centres in the same country [16] and differences in phenotype were identified [17]. Analyses of other international cohorts also show a marked heterogeneity across severe asthma patients. The pan-European U-BIOPRED cohort has provided evidence for the existence of different phenotypes and endotypes of severe asthma as well as evidence for ‘cluster-migrating’ patients [18]. The American Severe Asthma Research Program (SARP) cohort has also shown that heterogeneity exists even within clinical clusters [19]. Our present study further confirms that the severe asthma phenotype may be an oversimplification of the clinical reality and that different phenotypes with different therapeutic needs exist within the population of severe asthma patients currently viewed as a single group. Large differences in prevalence of severe asthma that have been described [20] support the idea that current guidelines may be ambiguous.

Strengths/limitations

This first ever attempt to integrate registry data across Europe has limitations. With over 3,000 patients included in the analysis, this is one of the largest comparisons of this population to date, providing insight into the characteristics and treatments of this heterogeneous group across Europe. With representation from South-, West-, Eastern- and Northern Europe there is a good geographical distribution and thus, the influence of differences in environmental and genetic factors and in healthcare systems have been incorporated but to what extent these influence the observed heterogeneity is unclear.
Perhaps the biggest, but inevitable, weakness is the retrospective nature of the study. Indeed, there was significant variation in inclusion criteria and only half the registries used the joint ERS/ATS definition of severe asthma. Furthermore, not all patients were treated in a specialized asthma centre while half the registries solely included patients in tertiary care, reflecting diversity in what clinicians in different European countries consider to be severe asthma. A further important limitation of the current data is preselection of specific patient subgroups; particularly the registries in Netherlands, Sweden and Slovenia focused on including patients that were starting biological therapies which is expected to result in cohorts composed of the most severe patients. However, we expected this preselection of more severe patients to be reflected in a selection of patients who met the current international guidelines but that was not the case. Some registries, i.e. Sweden and Belgium, are currently run in only one city or even one hospital, which implies that data not necessarily reflects a country but sometimes a specific situation in a country.

Conclusion

In summary, this study shows that the population of severe asthma patients in Europe is heterogeneous and differs in both clinical characteristics and treatment. These results lead to several key implications. First, severe asthma populations and treatment, even when biological users are excluded, greatly differ between countries. Thus, results from single centre trials, or even multicentre trials in the same country, cannot necessarily be extrapolated to other countries. Second, the definition of severe asthma in current guidelines does not comply with characteristics of real-world severe asthma patients; therefore, there might be differences in the application of these guidelines in the different countries. Third, the first key messages underline the importance of harmonization of severe asthma databases across Europe and the need for long-term follow-up of the patient. A consensus on the data that must be collected to provide solutions to these challenges should be agreed and this will provide a logical next step for the SHARP consortium. Of importance to future
research in the SHARP CRC, the use of aggregated data proved to be a relatively easy way to obtain data that can be used for international collaboration.

Acknowledgements

The authors would like to thank Elise Heuvelin (ERS office) for her much appreciated support in collecting the data.

Members of the SHARP CRC are: B. Abenhardt, Praxis Dr. Abenhardt und Jochen Hinrichs-Pavlik, Heidelberg, Germany; I. Adcock, National Heart and Lung Institute, Imperial College London, London, United Kingdom; J. Adler, European Lung Foundation, Sheffield, UK; R. Alfonso, GSK, USA; R. Ali, Barts Health NHS Trust, UK; S. Alkameh, Lungenfachpraxis Backnang, Backnang, Germany; C. Almonacid Sánchez, Hospital Ramón y Cajal, Madrid, Spain; L. Alvares, Novartis Pharma AG, Basel, Switzerland; G. Anderson, University of Melbourne, Melbourne, Australia; K. Assing, Department of Respiratory Medicine, Aalborg; University Hospital, Denmark; S. Ayre, European Lung Foundation, Sheffield, UK; J. Becker, Facharztpraxis für Pneumologie, Lübeck, Germany; E. Bel, Amsterdam UMC, University of Amsterdam, Department of Respiratory Medicine, Amsterdam, The Netherlands; K. Bergmann, Charité Berlin Allergie-Centrum, Berlin, Germany; K. Bieksiene, Lithuanian University of Health Science, Kaunas, Lithuania; N. Bjerring, Department Respiratory Medicine, Odense University Hospital, Odense, Denmark; F. Blasi, Milano Respiratory Unit and Adult Cystic Fibrosis Center, and Department of Pathophysiology and Transplantation, University of Milan, Milan, Italy; P. Bloemen, Respiratory Medical Affairs, GSK, The Netherlands; H. Blum, MECS Dortmund GmbH, Dortmund, Germany; S. Böing, Pneumoplus, Lungen- und Allergiezentrum, Neuss, Germany; M. Bonavia, Respiratory Rehabilitation, ASL3, Genoa, Italy; A. Bossios, ivision of Respiratory Medicine and Allergy, Department of Medicine, Karolinska University Hospital, Huddinge, Sweden; A. Bourdin, PhyMedExp, INSERM, EFS, Université de Montpellier, CHU Montpellier, Montpellier, France; G. Braunstahl, Sint Franciscus Gasthuis & Vlietland, Department of Pulmonology,
Rotterdam, The Netherlands; A. Brons, European Lung Foundation, Sheffield, UK; G. Brusselle, University of Ghent, UZ Ghent, Ghent; J. Buis, TEVA Pharmaceuticals, Amsterdam, The Netherlands; J. Busby, Queen's University Belfast, Belfast, United Kingdom; M. Caiaffa, University of Foggia, Department of Medical Sciences and Surgery, School and Chair of Allergology and Clinical Immunology, Foggia, Italy; C. Calabrese, Department of Translational Medical Sciences, University of Campania "L. Vanvitelli", Caserta, Italy; G. Camiciottoli, Dept. Experimental and Clinical Biomedical Sciences "Mario Serio", Respiratory Unit, Careggi University Hospital, Florence, Italy; G. Canonica, Personalized Medicine Clinic, Asthma and Allergy, Humanitas Clinical and Research Center, Humanitas University, Rozzano and SANI-Severe Asthma Network Italy, Milan, Italy; H. Cao, Novartis Pharmaceuticals Corporation, East Hanover, NJ, United States; C. Caruso, Allergy unit, Fondazione Policlinico A. Gemelli, IRCCS, Rome, Italy; M. Castilla Martínez, Hospital Los Arcos del Mar Menor, Murcia, Spain; S. Centanni, Dpt of Health Sciencies, Università degli Studi Milano, Respiratory Unit, ASST Santi Paolo e Carlo, Milan, Italy; K. Chung, Airway Disease, National Heart & Lung Institute, Imperial College London, London, United Kingdom; C. Cisneros Serrano, Hospital de La Princesa, Madrid, Spain; A. Corsico, Division of Respiratory Diseases, IRCCS Policlinico San Matteo Foundation and Department of Internal Medicine and Therapeutics, University of Pavia, Pavia, Italy; L. Cosmi, Department of Experimental and Clinical Medicine, University of Florence, Florence, Italy; M. Costantino, Allergy and Clinical Immunology Unit, Department of Medicine, "Carlo Poma" Hospital Mantova, Mantova, Italy; R. Costello, Royal College of Surgeons in Ireland, Beaumont Hospital, Dublin, Ireland; N. Crimi, Division of Pneumology and Allergology, University of Catania, Catania, Italy; Z. Csoma, National Koranyi Institute of Pulmonology, Budapest, Hungary; S. Dahlen, Karolinska Institutet, Stockholm, Sweden; B. Dählén, Division of Respiratory Medicine and Allergy, Department of Medicine, Karolinska University Hospital, Huddinge, Sweden; M. D'Amato, Respiratory Department, Division of Respiratory Diseases, "Federico II" University, AO Dei Colli, Naples, Italy; D. Davies, Southampton University Hospital, Southampton, UK; E. Davin, European Lung Foundation, Sheffield, UK; F. de Borja
García-Cosío Piqueras, Hospital Son Espases Palma Mallorca, Islas Baleares, Spain; G. Decarlo, European Federation of Allergy and Airways Diseases (EFA), Brussels, Belgium; A. Deimling, Lungenpraxis Schleswig, Schleswig, Germany; S. Del Giacco, Department of Medical Sciences and Public Health, University of Cagliari, Cagliari, Italy; R. Diaz Campos, Hospital 12 Octubre, Madrid, Spain; M. Djandji, Medical Affairs, Sanofi Genzyme, Cambridge, MA, USA; R. Djukanovic, NIHR Southampton Respiratory Biomedical Research Unit, Faculty of Medicine, University of Southampton, Southampton, United Kingdom; D. Doberer, Vienna General Hospital, Vienna, Austria; L. Dupont, University of Leuven, UZ Gasthuisberg Leuven, Belgium; K. Dyett, European Lung Foundation, Sheffield, UK; N. Edelbahrer, University Clinical Center Maribor, Pneumonology Department; M. Edelmann, Lungenpraxis Aalen, Aalen, Germany; R. Ehmann, Gemeinschaftspraxis für ambulante Pneumologie mit Allergiezentrum, Stuttgart, Germany; A. Ekberg-Jansson, Department of Research and Development, Region Halland, Sweden & The Sahlgrenska Academy, Institute of Medicine, University of Gothenburg, Gothenburg, Sweden; A. Farsi, SOS of Allergology and Clinical Immunology, Prato, Azienda USL Toscana Centro, Italy; E. Favero, Severe asthma multidisciplinary outpatient clinic, Vittorio Veneto Hospital, Treviso, Italy; J. Feimer, Pneumologie Odeonsplatz, München, Germany; M. Fletcher, Respiratory Medical Franchise, GSK, Brentford, United Kingdom; B. Foschino, Section of Respiratory Diseases, Medical and Surgical Sciences Department, University of Foggia, Foggia, Italy; B. Frankemölle, European Lung Foundation, Sheffield, UK; M. Gaga, Athens Chest Hospital Sotiria, Athens, Greece; M. Gappa, Marien-Hospital, Klinik für Kinder- und Jugendmedizin, Wesel, Germany; J. García de Pedro, Hospital Gregorio; Marañón, Madrid, Spain; J. García Rivero, Hospital Laredo, Cantabria, Spain; M. Gasplmayr, Kardiologische und fachinternistische ÜBAG Dr. Sandrock und Partner, Altdorf bei Nürnberg, Germany; R. Gebhardt, Dr. Rainer Gebhardt, Berlin, Germany; H. Geldmacher, Pneumologicum, Hannover, Germany; C. Geltner, Kreisklinik Bad Reichenhall, Abteilung für Pneumologie und Beatmungsmedizin, Bad Reichenhall, Germany; M. Gerstlauer, Klinikum Augsburg, II. Kinderklinik, Augsburg, Germany; T. Gibson, European Lung Foundation, Sheffield, UK; G.
Giuseppe, Allergy and Pneumology Unit, A.O. S.Croce e Carle, Cuneo, Italy; C. Gogoll, Evan. Elisabeth Klinik, Innere Medizin, Berlin, Germany; V. Grimm-Sachs, Praxis Dr. Grimm-Sachs, Bruchsal, Germany; I. Grisle, Riga Eastern Clinical University Hospital, Riga, Latvia; B. Grün, Praxis Dr. Grün, Bad Windsheim, Germany; A. Grünewaldt, Universitätsklinikum Frankfurt, Frankfurt, Germany; G. Guarnieri, Department of Cardiac-Thoracic-Vascular Sciences and Public Health, University of Padua, Padova, Italy; J. Gullón Blanco, Hospital San Agustín. Avilés, Asturias, Spain; E. Hamelmann, Klinik für Kinder- und Jugendmedizin Kinderzentrum Bethel, Bielefeld, Germany; D. Hamerlijnck, European Lung Foundation, Sheffield, UK; A. Hammers-Reinhard, Praxis Hammers-Reinhard, Homburg-Saar, Germany; S. Hanon, Free University Brussel, Academic Ziekenhuis, Jette, Bruxelles; S. Hansen, Respiratory Research Unit, Department of Respiratory Medicine, Bispebjerg University Hospital, Copenhagen, Denmark; D. Harzheim, Waldburg-Zeil Kliniken - Fachkliniken Wangen, Wangen im Allgäu, Germany; L. Heaney, Queens University Belfast, UK and Belfast Health & Social Care Trust UK; E. Heffler, Personalized Medicine Clinic, Asthma and Allergy, Humanitas Clinical and Research Center, Humanitas University, Rozzano and SANI-Severe Asthma Network Italy, Milan, Italy; S. Hellmich, Pneumologie am Schelztor Esslingen, Esslingen, Germany; M. Herden, Lungenfachärztlich-Internistische Schwerpunktpraxis, Freising, Germany; T. Hering, Arzt für Pneumologie, Allergologie, Schlafmedizin, Berlin, Germany; F. Herth, Thoraxklinik Heidelberg gGmbH, Heidelberg, Germany; O. Hilberg, Department of Respiratory Medicine, Vejle Hospital, Vejle, Denmark; I. Horvath, National Koranyi Institute of Pulmonology, Budapest, Hungary; P. Howarth, Respiratory Medical Franchise, GSK, Brentford, United Kingdom; M. Hubatsch, Lungenarztpraxis Dr. Hubatsch, Heilbronn, Germany; M. Humbert, Université Paris-Sud, Le Kremlin-Bicêtre, France; K. Husemann, MVZ Klinikum Kempten, Praxis für Pneumologie und Allergologie, Kempten, Germany; M. Idzko, Klinik für Pneumologie, Universitätsklinikum Freiburg, Freiburg, Germany; D. Jackson, Guy’s & St Thomas’ NHS Trust and King’s College London, UK; M. Jandl, Hamburger Institut für Therapieforschung GmbH, Hamburg, Germany; X. Jaumont, Novartis Pharma AG, Basel, Switzerland; G. Joos, department of
Pneumology, UZ Gent, University of gent, Belgium; M. Jöst, Malteser Lungen-und
Allergiezentrum Bonn, Bonn, Germany; M. Jüch, Pneumologische Praxis am Ulrichplatz,
Magdeburg, Germany; M. Kabesch, Krankenhaus Barmherzige Brüder Regensburg,
Regensburg, Germany; P. Kaiser-Labusch, Klinikum Bremen Mitte, Bremen, Germany; P.
Kardos, Studienzentrum Maingau, Frankfurt, Germany; F. Käßner, MECS Cottbus, Cottbus,
Germany; T. Keeley, Respiratory Medical Franchise, GSK, Brentford, United Kingdom; W.
Kerr, Respiratory Medical Franchise, GSK, Brentford, United Kingdom; J. Kirschner, CLMS
Studienzentrum Bamberg, GmbH, Bamberg, Germany; L. Klimek, Zentrum für Rhinologie
und Allergologie, Wiesbaden, Germany; M. Koca, Lungenpraxis Offenbach, Offenbach,
Germany; R. Koczulla, Schönklinik Berchtesgadener Land, Schönau am Königsee,
Germany; C. Koerner-Rettberg, Klinik für Kinder- und Jugendmedizin der RUB im St. Josef-
Hospital, Bochum, Germany; P. Kopac, University Clinic of Respiratory and Allergic
Diseases, Golnik, Slovenia; S. Korn, Universitätssmedizin Mainz, Mainz, Germany; S. Korn,
Schwerpunkt Pneumologie, Universitätssmedizin Mainz, Mainz, Germany; M. Kots, Chiesi
Farmaceutici, Global Clinical Development, Parma, Italy; J. Kronsbein,
Berufsgenossenschaftliches Univ.klinikum Bergmannsheil, Bochum, Germany; P. Kuna,
Department of Internal Medicine, Asthma and Allergy, Medical University of Lodz, Lodz,
Poland; I. Kupryś Lipinska, Division of Internal Medicine Asthma and Allergy Medical
University of Lodz, Poland; N. Kwon, Respiratory Medical Franchise, GSK, Brentford, United
Kingdom; M. Langer, Lungenpraxis Dr. Langer Tübingen, Tübingen, Germany; B.
Langeveld, Deventer Hospital, Deventer, the Netherlands; A. Lantz, Division of Respiratory
Medicine and Allergy, Department of Medicine, Karolinska University Hospital, Huddinge,
Sweden; N. Lazarinis, Division of Respiratory Medicine and Allergy, Department of Medicine,
Karolinska University Hospital, Huddinge, Sweden; Z. Lasic, University Clinical Center
Kragujevac, Kragujevac, Serbia; L. Lehtimäki, University of Tampere, Tampere, Finland; J.
Leuppi, University Clinic of Internal Medicine, Basel, Switzerland; C. Lombardi, Departmental
Unit of Allergology and Pneumology, Hospital Institute Fondazione Poliambulanza, Brescia,
Italy; M. Lommatzsch, Universität Rostock, Abteilung Pneumologie, Rostock, Germany; A.
López-Viña, Hospital Puerta Hierro. Majadahonda, Madrid, Spain; R. Louis, department of pneumology, CHU Liege, GIGA13 reserach group, University of Liège, Belgium; R. Luca, Fondazione Policlinico Universitario A. Gemelli, IRCCS, Catholic University Rome, Italy; D. Lúðvíksdóttir, Landspitali University Hospital, Reykjavik, Iceland; C. Lüttecke-Hecht, Lungenfacharztpraxis Dr. C. Lüttecke-Hecht, Mainz, Germany; L. Macchia, Dept. of Emergency and Organ Transplantation, School and Chair of Allergology and Clinical Immunology, University of Bari – Aldo Moro, Bari, Italy; T. Magni, Chiesi Farmaceutici, Global Clinical Development, Parma, Italy; A. Maitland-van der Zee, Amsterdam UMC, University of Amsterdam, Department of Respiratory Medicine, Amsterdam, The Netherlands; C. Martínez Rivera, Hospital Germans Trias i Pujol. Badalona, Barcelona; P. Mastoridis, Novartis Pharmaceuticals Corporation, East Hanover, NJ, United States; F. Mazza, Respiratory Unit, Presidio Ospedaliero di Pordenone, Pordenone, Italy; F. Menzella, Santa Maria Nuova Hospital, Azienda USL di Reggio Emilia IRCCS, Pneumology Unit, Reggio Emilia, Italy; A. Menzies-Gow, Royal Brompton Hospital and Imperial College London, UK; A. Michils, Hôpital Erasme, Bruxelles, Belgium; F. Mihăltan, Department of Pulmonology, University of Medicine and Pharmacy "Carol Davila", Bucharest, Romania; M. Milanese, Pulmonology Unit, ASL2 Savonese, Pietra ligure, Savona, Italy; K. Milger-Kneidinger, Klinikum der Universität München, München, Germany; J. Molinska, Division of Internal Medicine Asthma and Allergy Medical University of Lodz, Poland; I. Montagna, Chiesi Farmaceutici, Global Clinical Development, Parma, Italy; P. Montuschi, Department of Pharmacology, Faculty of Medicine, Catholic University of the Sacred Heart, Fondazione Policlinico Universitario Agostino Gemelli, IRCCS Largo Francesco, Vito, Rome, Italy; N. Mülleneisen, Asthma und Allergiezentrum, Leverskusen, Germany; M. Muñoz Esquerre, Hospital Bellvitge, Barcelona, Spain; A. Nanzer-Kelly, Guy’s & St Thomas’ NHS Trust and King’s College London, UK; N. Nenasheva, Russian Medical Academy for Postgraduate Education, Moscow, Russia; C. Neurohr, Klinik Schillerhöhe, Abteilung für Pneumologie und Beatmungsmedizin, Gerlingen, Germany; E. Nucera, Catholic University S.Heart, Fondazione policlinico Universitario A. Gemelli, IRCCS, Roma, Italy; J. Otker, European
Lung Foundation, Sheffield, UK; K. Oud, Hospital Gelderse Vallei, Ede, the Netherlands; P. Paggiaro, Department of Surgery, Medicine, Molecular Biology and Critical Care, University of Pisa, Pisa, Italy; R. Parente, Department of Medicine, Division of Allergy and Clinical Immunology, University of Salerno, Salerno, Italy; J. Parkinson, Asthma Org UK; G. Passalacqua, Allergy and Respiratory Diseases, IRCCS Policlinico San Martino, University of Genoa, Genoa, Italy; N. Patberg, Isala hospital, Zwolle, the Netherlands; V. Patella, Division of Allergy and Clinical Immunology, Department of Medicine ASL Salerno, "Santa Maria della Speranza" Hospital, Battipaglia, Salerno, Italy; O. Patino, TEVA Pharmaceuticals, Amsterdem, The Netherlands; T. Paulsson, Respiratory Medical Franchise, GSK, Brentford, United Kingdom; R. Peche, Hôpital Vésale, Charleroi; G. Pelaia, Department of Medical and Surgical Sciences, Section of Respiratory Diseases, University Magna Graecia of Catanzaro, Catanzaro, Italy; E. Peress, Novartis Pharma AG, Basel, Switzerland; L. Pérez de Llano, Hospital Lucus Augusti, Lugo, Spain; P. Pfeffer, Barts Health NHS Trust and Barts and The London School of Medicine and Dentistry, Queen Mary University of London, UK; P. Pfister, Novartis Pharma AG, Basel, Switzerland; C. Pilette, CHU saint Luc, Université Catholique de Louvain, Belgium; C. Pinedo Sierra, Hospital San Carlos, Madrid, Spain; L. Pini, Department of Clinical and Experimental Sciences, University of Brescia, Spedali Civili di Brescia, Brescia, Italy; V. Plaza, Respiratory Medicine Department & Biomedical Research Institute, Hospital de la Santa Creu i Sant Pau, Universitat Autònoma de Barcelona, Barcelona, Spain; C. Porsbjerg, Respiratory Research Unit, Department of Respiratory Medicine, Bispebjerg University Hospital, Copenhagen, Denmark; F. Powitz, Pneumologie Elisenhof München, München, Germany; D. Ramos-Barbon, Respiratory Medicine Department & Biomedical Research Institute, Hospital de la Santa Creu i Sant Pau, Universitat Autònoma de Barcelona, Barcelona, Spain; T. Ranger, European Lung Foundation, Sheffield, UK; L. Rasmussen, Allergy Clinic, Copenhagen University Hospital Gentofte, Gentofte, Denmark; K. Rasmussen, Department of Respiratory Medicine, Zealand University Hospital, Roskilde, Denmark; M. Rezelj, University Clinic of Respiratory and Allergic Diseases, Goñik, Slovenia; L. Ricciardi, Allergy and Clinical
Immunology Unit, University Hospital "G.Martino", Department of Clinical and Experimental Medicine, University of Messina, Italy; F. Ricciardolo, Department of Clinical and Biological Sciences, University of Torino, San Luigi Hospital, Orbassano, Torino, Italy; L. Richards, Amsterdam UMC, University of Amsterdam, Department of Respiratory Medicine, Amsterdam, The Netherlands; E. Ridolo, Department of Medicine and Surgery, University of Parma, Parma, Italy; L. Rijksenbeek-Nouwens, Dutch Asthma Centre Davos, Davos, Switzerland; G. Rolla, Allergy and Clinical Immunology, AO Mauriziano Hospital, University of Torino, Turin, Italy; D. Romero Ribate, Hospital La Paz, Madrid, Spain; S. Rüdiger, Universitätsklinikum Ulm, Ulm, Germany; G. Safioti, TEVA Pharmaceuticals, Amsterdam, The Netherlands; T. Sandström, Dept of Medicine, Dept of Public Health and Clinical Medicine Respiratory Medicine Unit, Umeå University, Umeå, Sweden; P. Santus, Department of Clinical and Biomedical Sciences, Università degli Studi di Milano, Division of Respiratory Diseases, Sacco University Hospital, ASST Fatebenefratelli-Sacco, Milano, Italy; R. Sauer, Lungenzentrum Ulm, Ulm, Germany; G. Schauerte, CJD Berchtesgaden, Asthmazentrum und Diabetesszentrum, Berchtesgaden, Germany; R. Schipmann, Klinik Martinusquelle, Bad Lippspringe, Germany; F. Schleich, University of Liege, CHU Liege, Liege, Belgium; J. Schmid, Department of Respiratory Diseases and Allergy, Aarhus University Hospital, Aarhus, Denmark; F. Schmidt, Pneumologische Gemeinschaftspraxis Dr. Schmidt und Weeg, München, Germany; O. Schmidt, Lungenfachärzte KSS, Koblenz, Germany; M. Schmitz, Pneumo Westpfalz, Kaiserslautern, Germany; T. Schrag, Praxis Dr.med. Till Schrag, Bad Reichenhall, Germany; S. Schröer, Internistische Schwerpunktpraxis, Villingen-Schwenningen, Germany; K. Schultz, Klinik Bad Reichenhall, Bad Reichenhall, Germany; C. Schulz, Universitätsklinikum Regensburg, Regensburg, Germany; N. Scichilone, Division of Respiratory Diseases, Department of Promoting Health, Maternal-Infant. Excellence and Internal and Specialized Medicine (Promise) G. D'Alessandro, University of Palermo, Palermo, Italy; V. Sedlak, Czech Pneumology and Phthisiology Society, Prague, Czech Republic; J. Selb, University Clinic of Respiratory and Allergic Diseases, Gołnik, Slovenia; G. Senna, Allergy Unit, Asthma Center University-
Hospital of Verona, Verona, Italy; S. Sergejeva, University of Tartu, Tartu, Estonia; J.
Serrano Pariente, Hospital Inca, Islas Baleares, Spain; M. Sichau, MVZ für Diagnostik und
Therapie, Herne, Germany; D. Simona, Allergology Unit, AV3 ASUR Marche, Hospital
Civitanova Marche, Macerata, Italy; A. Singer, Barts Health NHS Trust, UK; D. Skowasch,
Universitätsklinikum Bonn, Bonn, Germany; S. Škrget, University Clinic of Respiratory and
Allergic Diseases, Golnik, Slovenia; F. Smeenk, Catharina hospital, Eindhoven, the
Netherlands; S. Smith, GSK, USA; P. Solidoro, Professor of Respiratory Medicine, Dept. of
Medical Sciences, University of Turin, Turin, Italy; J. Sont, Leiden University Medical Centre,
Department of Biomedical Data Sciences, section Medical Decision Making, Leiden, The
Netherlands; G. Spadaro, Department of internal medicine, clinical immunology, clinical
pathology and infectious diseases, Azienda ospedaliera universitaria Federico II, Naples,
Italy; A. Spanevello, University of Insubria, Varese, ICS Maugeri, IRCCS, Tradate, Italy; A.
Spanevello, Istituti Clinici Scientifici Maugeri IRCCS, Tradate, Italy; University of Insubria,
Varese, Italy; M. Stefansdottir, European Lung Foundation, Sheffield, UK; K. Steinmetz,
Gemeinschaftspraxis, Darmstadt, Germany; J. Steiß, Universitätsklinikum Giessen, Giessen,
Germany; M. Stephan, Klinik Löwenstein, Löwenstein, Germany; S. Stieglitz, Wuppertaler
Lungenzentrum, Wuppertal, Germany; H. Suhtling, MH Hannover, Hannover, Germany; C.
Taube, Universitätsmedizin Essen, Westdeutsches Lungenzentrum am Universitätsklinikum
Essen gGmbH, Essen, Germany; A. ten Brinke, Medical Centre Leeuwarden, Leeuwarden,
The Netherlands; S. Tolga Yavuz, Zentrum für Kinderheilkunde, Universitätsklinikum Bonn,
Bonn, Germany; N. Tudoric, Dubrava University Hospital, Zagreb, Croatia; C. Ulrik,
Department of Respiratory Medicine, Hvidovre University Hospital, Copenhagen, Denmark;
J. van Bragt, Amsterdam UMC, University of Amsterdam, Department of Respiratory
Medicine, Amsterdam, The Netherlands; M. van de Ven, Rijnstate Hospital, Arnhem, The
Netherlands; F. van den Elshout, Rijnstate Hospital, Arnhem, The Netherlands; M. Van
Dyke, GSK, USA; S. van Nederveen-Bendien, Haga hospital, the Hague, The Netherlands; I.
van Veen, Medisch Spectrum Twente, Enschede, The Netherlands; O. vandenplas, CHU
Godine Namur, Belgium; K. Velthove, Respiratory Medical Affairs, GSK, The Netherlands; A.
Vianello, Respiratory Pathophysiology Division, Department of Cardiac, Thoracic and Vascular Sciences, University of Padova, Padova, Italy; S. Vijverberg, Amsterdam UMC, University of Amsterdam, Department of Respiratory Medicine, Amsterdam, The Netherlands; C. Vogelberg, Universitätsklinikum Carl Gustav Carus, Klinik und Poliklinik für Kinder- und Jugendmedizin, Dresden, Germany; S. Wagers, BioSciConsulting, Maasmechelen, Belgium; E. Wallén-Nielsen, Division of Respiratory Medicine and Allergy, Department of Medicine, Karolinska University Hospital, Huddinge, Sweden; E. Weersink, Amsterdam UMC, University of Amsterdam, Department of Respiratory Medicine, Amsterdam, The Netherlands; T. Wisskirchen, Aeroprax, Wuppertal, Germany; M. Yacoub, Allergology Unit, San Raffaele Hospital of Milano, Milan, Italy; S. Yancey, GSK, USA; V. Yasinska, Division of Respiratory Medicine and Allergy, Department of Medicine, Karolinska University Hospital, Huddinge, Sweden; M. Zappa, Pulmonology Department, Sandro Pertini Hospital, Rome, Italy; S. Zielen, Universitätsklinikum Frankfurt, Frankfurt, Germany; C. Zimmermann, Pneumologische Praxis Reutlingen, Reutlingen, Germany; R. Zimmermann, Klinikum Landshut, Med. Klinik 2, Landshut, Germany.
Tables

Table 1. Abbreviations of country names, as used in this paper.

<table>
<thead>
<tr>
<th>Country name</th>
<th>Abbreviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Belgium</td>
<td>BE</td>
</tr>
<tr>
<td>Denmark</td>
<td>DM</td>
</tr>
<tr>
<td>Germany</td>
<td>DE</td>
</tr>
<tr>
<td>Hungary</td>
<td>HU</td>
</tr>
<tr>
<td>Italy</td>
<td>IT</td>
</tr>
<tr>
<td>Poland</td>
<td>PL</td>
</tr>
<tr>
<td>Slovenia</td>
<td>SL</td>
</tr>
<tr>
<td>Spain</td>
<td>ES</td>
</tr>
<tr>
<td>Sweden</td>
<td>SE</td>
</tr>
<tr>
<td>The Netherlands</td>
<td>NL</td>
</tr>
<tr>
<td>The United Kingdom</td>
<td>UK</td>
</tr>
</tbody>
</table>
Table 2. Baseline characteristics of patients included in different severe asthma registries that are part of SHARP.

<table>
<thead>
<tr>
<th></th>
<th>United Kingdom</th>
<th>Belgium</th>
<th>Italy</th>
<th>Spain</th>
<th>The Netherlands</th>
<th>Germany</th>
<th>Poland</th>
<th>Slovenia</th>
<th>Hungary</th>
<th>Denmark</th>
<th>Sweden</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients, n</td>
<td>765</td>
<td>629</td>
<td>434</td>
<td>410</td>
<td>237</td>
<td>209</td>
<td>193</td>
<td>140</td>
<td>130</td>
<td>59</td>
<td>27</td>
</tr>
<tr>
<td>Age, years (SD)</td>
<td>47.6 (14.5)</td>
<td>56.9 (14.7)</td>
<td>54.1 (13.7)</td>
<td>56.4 (14.8)</td>
<td>52.8 (14.2)</td>
<td>44.4 (20.4)</td>
<td>48.4 (14.6)</td>
<td>53.5 (12.8)</td>
<td>58.3 (12.9)</td>
<td>51.9 (16.1)</td>
<td>50.8 (6.6)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>285 (37.5)</td>
<td>265 (42.1)</td>
<td>183 (41.9)</td>
<td>133 (52.4)</td>
<td>112 (47.3)</td>
<td>58 (46.9)</td>
<td>76 (39.4)</td>
<td>42 (30)</td>
<td>42 (32.3)</td>
<td>28 (47.5)</td>
<td>14 (51.9)</td>
</tr>
<tr>
<td>Smoking status, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>20 (4.1)</td>
<td>60 (9.3)</td>
<td>12 (2.7)</td>
<td>29 (7.1)</td>
<td>2 (0.9)</td>
<td>5 (2.4)</td>
<td>0 (0)</td>
<td>1 (0.7)</td>
<td>8 (6.2)</td>
<td>2 (4.0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Never-smoker</td>
<td>526 (71.7)</td>
<td>368 (58.5)</td>
<td>352 (80.5)</td>
<td>281 (68.5)</td>
<td>138 (57.9)</td>
<td>125 (59.8)</td>
<td>171 (88.6)</td>
<td>92 (65.7)</td>
<td>108 (83.1)</td>
<td>24 (48.0)</td>
<td>16 (59.3)</td>
</tr>
<tr>
<td>Ex-smoker</td>
<td>178 (24.3)</td>
<td>201(32.0)</td>
<td>73 (16.7)</td>
<td>100 (24.4)</td>
<td>97 (41.3)</td>
<td>79 (37.8)</td>
<td>22 (11.4)</td>
<td>47 (33.5)</td>
<td>14 (10.8)</td>
<td>19 (38.0)</td>
<td>11 (40.7)</td>
</tr>
<tr>
<td>Pack-years, median (IQR)</td>
<td>15 (5-20)</td>
<td>15 (6-27)</td>
<td>9 (4-15)</td>
<td>19 (10-23)</td>
<td>10 (4-19)</td>
<td>8 (2-15)</td>
<td>12.5 (15)</td>
<td>10 (3-20)</td>
<td>&lt;5 PY</td>
<td>8.5 (2.2-15)</td>
<td>5 (4-9)</td>
</tr>
<tr>
<td>BMI, kg/m² (SD)</td>
<td>30.6 (7.4)</td>
<td>27.7 (12.6)</td>
<td>26.2 (5.0)</td>
<td>28.2 (5.0)</td>
<td>28.3 (5.4)</td>
<td>27.4 (10.8)</td>
<td>28.1</td>
<td>27.1 (5.8)</td>
<td>26.9 (5.4)</td>
<td>27.1 (5.4)</td>
<td>27.7 (5.3)</td>
</tr>
<tr>
<td>FEV₁, %predicted (SD)</td>
<td>67.8 (22.8)</td>
<td>67.9 (21.0)</td>
<td>71.4 (20.2)</td>
<td>68.1 (36.1)</td>
<td>76.9 (22.2)</td>
<td>70.3 (23.0)</td>
<td>63.2 (23.5)</td>
<td>69.6 (19.8)</td>
<td>56.0 (16.8)</td>
<td>72.0 (19.1)</td>
<td>66.0 (19.9)</td>
</tr>
<tr>
<td>PVC, %predicted (SD)</td>
<td>85.3 (19.8)</td>
<td>88.2 (20.2)</td>
<td>88.2 (21.1)</td>
<td>NA</td>
<td>98.8 (20.5)</td>
<td>84.5 (19.7)</td>
<td>NA</td>
<td>95.0 (15.8)</td>
<td>76.6 (18.5)</td>
<td>78.2 (18.3)</td>
<td>86.8 (19.6)</td>
</tr>
<tr>
<td>Eosinophils x10⁹ cells/l, median (IQR)</td>
<td>0.300 (0.200-0.600)</td>
<td>0.280 (0.225-0.599)</td>
<td>0.540 (0.190-0.645)</td>
<td>0.310 (0.100-0.530)</td>
<td>0.290 (0.105-0.570)</td>
<td>0.230 (0.100-0.580)</td>
<td>0.410 (0.200-0.740)</td>
<td>0.210 (0.100-0.600)</td>
<td>0.345 (0.140-0.578)</td>
<td>0.250 (0.100-0.600)</td>
<td>0.800 (0.600-1.000)</td>
</tr>
<tr>
<td>Neutrophils x10⁹ cells/l, median (IQR)</td>
<td>NA</td>
<td>NA</td>
<td>4.75 (3.12-5.66)</td>
<td>NA</td>
<td>5.48 (4.09-7.23)</td>
<td>5.02 (3.71-7.15)</td>
<td>NA</td>
<td>5.18 (3.60-6.80)</td>
<td>5.26 (3.98-7.37)</td>
<td>NA</td>
<td>3.80 (2.90-5.10)</td>
</tr>
<tr>
<td>Total IgE IU/ml, median (IQR)</td>
<td>165 (55.9-491)</td>
<td>150 (68.0-513)</td>
<td>272 (122-561)</td>
<td>236 (102-516)</td>
<td>144 (49-368)</td>
<td>119 (78.0-579)</td>
<td>167.5 (159)</td>
<td>238 (115-358)</td>
<td>164 (54.7-385)</td>
<td>164 (74.3-283)</td>
<td>275 (135-820)</td>
</tr>
<tr>
<td>FeNO ppb, median (IQR)</td>
<td>41 (23-77)</td>
<td>25 (14-42)</td>
<td>32 (17-64)</td>
<td>33 (19-52)</td>
<td>33 (20-60)</td>
<td>33 (18-79)</td>
<td>27 (27)</td>
<td>66 (27-101)</td>
<td>32 (18-56)</td>
<td>26 (13-49)</td>
<td>57 (29-80)</td>
</tr>
<tr>
<td>Adult-onset asthma, n (%)</td>
<td>385 (59.8)</td>
<td>202 (31.8)</td>
<td>101 (24.0)</td>
<td>NA</td>
<td>129 (63.2)</td>
<td>65 (39.4)</td>
<td>68 (55.2)</td>
<td>110 (78)</td>
<td>89 (68.5)</td>
<td>26 (76)</td>
<td>24 (89.9)</td>
</tr>
<tr>
<td>ACC, mean (SD)</td>
<td>3.0 (1.3)</td>
<td>2.5 (1.3)</td>
<td>2.9 (1.3)</td>
<td>NA</td>
<td>2.1 (1.2)</td>
<td>2.6 (1.5)</td>
<td>3.3 (0.9)</td>
<td>NA</td>
<td>NA</td>
<td>2.4 (1.4)</td>
<td>1.8 (1)</td>
</tr>
<tr>
<td>ACT, mean (SD)</td>
<td>NA</td>
<td>1.9 (2.4)</td>
<td>17.2 (5.4)</td>
<td>15.9 (5.8)</td>
<td>NA</td>
<td>15 (6.0)</td>
<td>12.3</td>
<td>16.7 (5.5)</td>
<td>16.6 (1.2)</td>
<td>NA</td>
<td>12 (3.8)</td>
</tr>
<tr>
<td>Uncontrolled based on ACC/ACT, n (%)</td>
<td>591 (94.6)</td>
<td>331 (76.1)</td>
<td>250 (54.6)</td>
<td>221 (68.8)</td>
<td>88 (61.5)</td>
<td>135 (71.1)</td>
<td>191 (99)</td>
<td>87 (64.0)</td>
<td>130 (100)</td>
<td>21 (70)</td>
<td>27 (100)</td>
</tr>
<tr>
<td>Hospitalization last year, n (%)</td>
<td>251 (39.5)</td>
<td>229 (36)</td>
<td>53 (17.6)</td>
<td>52 (12.7)</td>
<td>NA</td>
<td>55 (32.4)</td>
<td>78 (40.5)</td>
<td>61 (47.2)</td>
<td>36 (28)</td>
<td>16 (40)</td>
<td>1 (3.7)</td>
</tr>
<tr>
<td>Included in, n (%)</td>
<td>Primary care</td>
<td>Secondary care</td>
<td>Tertiary care</td>
<td>NA</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>-------------------</td>
<td>--------------</td>
<td>----------------</td>
<td>---------------</td>
<td>----</td>
<td>-------</td>
<td>-------</td>
<td>-------</td>
<td>-------</td>
<td>-------</td>
<td>-------</td>
<td>-------</td>
</tr>
<tr>
<td>GINA 4 treatment, n (%)</td>
<td>162 (21.2)</td>
<td>309 (49.0)</td>
<td>18 (5.7)</td>
<td>197 (48.1)</td>
<td>113 (47.7)</td>
<td>130 (62.2)</td>
<td>59 (27.5)</td>
<td>87 (62.6)</td>
<td>93 (73.5)</td>
<td>24 (49.0)</td>
<td>15 (55.6)</td>
</tr>
<tr>
<td>GINA 5 treatment, n (%)</td>
<td>569 (74.4)</td>
<td>320 (51.0)</td>
<td>297 (94.3)</td>
<td>210 (51.2)</td>
<td>118 (49.8)</td>
<td>79 (17.8)</td>
<td>140 (72.5)</td>
<td>52 (74.4)</td>
<td>37 (28.5)</td>
<td>14 (28.6)</td>
<td>12 (44.4)</td>
</tr>
<tr>
<td>Biological use, n (%)</td>
<td>479 (64.5)</td>
<td>160 (25.0)</td>
<td>215 (49.5)</td>
<td>210 (51.2)</td>
<td>82 (34.6)</td>
<td>80 (38.3)</td>
<td>157 (71.0)</td>
<td>66 (47.4)</td>
<td>30 (23.1)</td>
<td>59 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Anti-IgE</td>
<td>115 (25.4)</td>
<td>130 (21.0)</td>
<td>180 (41.2)</td>
<td>197 (48.1)</td>
<td>29 (12.2)</td>
<td>41 (19.6)</td>
<td>129 (66.8)</td>
<td>59 (42.4)</td>
<td>16 (12.3)</td>
<td>18 (30.5)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Anti-Ix</td>
<td>337 (74.6)</td>
<td>30 (5.0)</td>
<td>35 (8.1)</td>
<td>13 (3.2)</td>
<td>53 (22.4)</td>
<td>39 (18.7)</td>
<td>8 (4.1)</td>
<td>7 (5.0)</td>
<td>14 (10.8)</td>
<td>41 (69.5)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Thermoplasty, n (%)</td>
<td>1 (0.2)</td>
<td>0 (0)</td>
<td>NA</td>
<td>0 [0.0]</td>
<td>0 [0.0]</td>
<td>NA</td>
<td>0 [0.0]</td>
<td>0 [0.0]</td>
<td>0 [0.0]</td>
<td>0 [0.0]</td>
<td>0 [0.0]</td>
</tr>
<tr>
<td>High altitude treatment, n (%)</td>
<td>0 [0.0]</td>
<td>9 (1.4)</td>
<td>NA</td>
<td>0 [0.0]</td>
<td>3 [1.3]</td>
<td>NA</td>
<td>0 [0.0]</td>
<td>2 [1.4]</td>
<td>0 [0.0]</td>
<td>0 [0.0]</td>
<td>0 [0.0]</td>
</tr>
<tr>
<td>ICS* mean dose (SD)</td>
<td>NA</td>
<td>0 (0)</td>
<td>NA</td>
<td>0 (0)</td>
<td>33 (14)</td>
<td>NA</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>NA</td>
<td>0 (0)</td>
</tr>
<tr>
<td>OCS* Mean dose, median [IQR]</td>
<td>10.0 (10.0-20.0)</td>
<td>9.0 (5.0-10.0)</td>
<td>10.7 (5.0-20.0)</td>
<td>10.0 (5.0-5.0)</td>
<td>10.0 (5.0-5.0)</td>
<td>10.0 (5.0-5.0)</td>
<td>10.0 (5.0-15.0)</td>
<td>7.0 (5.0-10.0)</td>
<td>7.5 (5.0-10.0)</td>
<td>NA</td>
<td>10.0 (7.5-10.0)</td>
</tr>
</tbody>
</table>

Data are represented as mean with standard deviation (SD) unless otherwise specified. IQR: Interquartile range from quartile 1 – quartile 3, BMI: body mass index, FEV1: Forced expiratory volume in one second, FVC: Forced vital capacity, FeNO: fraction of exhaled Nitric Oxide, ACQ: asthma control questionnaire, ACT: asthma control test, GINA: Global Initiative for asthma, ICS: inhalation corticosteroids, OCS: oral corticosteroids. *: dose expressed as fluticasone equivalents, #: dose expressed as prednisone equivalents.
Table 3. Medication prior to starting (or >6 months after stopping) of high-cost therapy [biologicals, bronchial thermoplasty, high-altitude treatment].

<table>
<thead>
<tr>
<th>Medication use</th>
<th>United Kingdom</th>
<th>Belgium</th>
<th>Italy</th>
<th>Spain</th>
<th>Poland</th>
<th>The Netherlands</th>
<th>Hungary</th>
<th>Slovenia</th>
<th>Denmark</th>
<th>Sweden</th>
<th>Germany</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>477</td>
<td>469</td>
<td>219</td>
<td>210</td>
<td>183</td>
<td>143</td>
<td>100</td>
<td>73</td>
<td>49</td>
<td>27</td>
</tr>
<tr>
<td><strong>GINA step 4, n (%)</strong></td>
<td>152 (31.9)</td>
<td>347 (74)</td>
<td>2 (2.0)</td>
<td>166 (79.9)</td>
<td>53 (27.5)</td>
<td>34 (17.8)</td>
<td>74 (74.0)</td>
<td>42 (57.5)</td>
<td>24 (48)</td>
<td>15 (55.6)</td>
<td>NA</td>
</tr>
<tr>
<td><strong>GINA step 5, n (%)</strong></td>
<td>325 (68.1)</td>
<td>109 (23)</td>
<td>98 (98.0)</td>
<td>44 (20.9)</td>
<td>140 (72.5)</td>
<td>87 (60.8)</td>
<td>26 (26.0)</td>
<td>31 (42.4)</td>
<td>14 (29)</td>
<td>12 (44.4)</td>
<td>NA</td>
</tr>
<tr>
<td><strong>SABA, n (%)</strong></td>
<td>444 (93.3)</td>
<td>377 (90.2)</td>
<td>4 (4.0)</td>
<td>32 (15.2)</td>
<td>193 (100)</td>
<td>107 (74.8)</td>
<td>100 (100)</td>
<td>43 (58.9)</td>
<td>29 (59.2)</td>
<td>27 (100)</td>
<td>NA</td>
</tr>
<tr>
<td><strong>SAMA, n (%)</strong></td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>175 (15.5)</td>
<td>38 (19.7)</td>
<td>25 (17.5)</td>
<td>0 (0)</td>
<td>28 (38.0)</td>
<td>1 (2.0)</td>
<td>8 (29.6)</td>
<td>NA</td>
</tr>
<tr>
<td><strong>LABA, n (%)</strong></td>
<td>436 (92.2)</td>
<td>457 (97.4)</td>
<td>219 (100)</td>
<td>206 (97.2)</td>
<td>155 (80.3)</td>
<td>135 (94.4)</td>
<td>100 (100)</td>
<td>72 (98.0)</td>
<td>43 (87.8)</td>
<td>27 (100)</td>
<td>NA</td>
</tr>
<tr>
<td><strong>LAMA, n (%)</strong></td>
<td>269 (56.8)</td>
<td>113 (24.1)</td>
<td>40 (40.4)</td>
<td>35 (28.9)</td>
<td>37 (19.2)</td>
<td>42 (29.4)</td>
<td>14 (14)</td>
<td>54 (73.9)</td>
<td>22 (44.9)</td>
<td>8 (30)</td>
<td>NA</td>
</tr>
<tr>
<td><strong>ICS, n (%)</strong></td>
<td>477 (100)</td>
<td>457 (97.4)</td>
<td>219 (100)</td>
<td>212 (100)</td>
<td>193 (100)</td>
<td>142 (99.3)</td>
<td>100 (100)</td>
<td>73 (100)</td>
<td>46 (93.9)</td>
<td>27 (100)</td>
<td>NA</td>
</tr>
<tr>
<td><em><em>ICS mean dose</em>, µg/day (SD)</em>*</td>
<td>973 (508)</td>
<td>986 (479)</td>
<td>570 (497)</td>
<td>1320 (685)</td>
<td>1220 (668)</td>
<td>1178 (797)</td>
<td>909 (386)</td>
<td>700.1 (207.4)</td>
<td>1073 (372)</td>
<td>1196 (641)</td>
<td>NA</td>
</tr>
<tr>
<td><strong>LTRA, n (%)</strong></td>
<td>188 (41.6)</td>
<td>25 (5.5)</td>
<td>37 (37.4)</td>
<td>123 (58.6)</td>
<td>128 (66.3)</td>
<td>29 (20.3)</td>
<td>45 (45.0)</td>
<td>301 (41.0)</td>
<td>28 (37.3)</td>
<td>21 (77.8)</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Theophylline, n (%)</strong></td>
<td>120 (25.3)</td>
<td>65 (14.0)</td>
<td>7 (7.1)</td>
<td>22 (11.2)</td>
<td>52 (26.9)</td>
<td>6 (4.2)</td>
<td>35 (35.0)</td>
<td>1 (1.3)</td>
<td>5 (10.2)</td>
<td>2 (7.4)</td>
<td>NA</td>
</tr>
<tr>
<td><strong>OCS maintenance</strong></td>
<td>n (%)</td>
<td>325 (68.1)</td>
<td>102 (22.0)</td>
<td>105 (71.9)</td>
<td>45 (12.3)</td>
<td>87 (45.1)</td>
<td>88 (60.8)</td>
<td>26 (26.0)</td>
<td>31 (42.4)</td>
<td>NA</td>
<td>17 (63.0)</td>
</tr>
<tr>
<td><strong>DDD (SD)</strong></td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>1.81 (0.90)</td>
<td>NA</td>
<td>1.4 (1.1)</td>
<td>0.67 (0.34)</td>
<td>NA</td>
<td>0.94 (0.29)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td><strong>Dose</strong></td>
<td>10.0 (10.0)</td>
<td>10.0 (5.0)</td>
<td>10.0 (5.0)</td>
<td>10.0 (5.0)</td>
<td>10.0 (7.0)</td>
<td>10.0 (10.0)</td>
<td>10.0 (10.0)</td>
<td>10.0 (10.0)</td>
<td>10.0 (10.0)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td><strong>NSAIDS, n (%)</strong></td>
<td>25 (5.0)</td>
<td>NA</td>
<td>NA</td>
<td>44 (22.8)</td>
<td>3 (1.2)</td>
<td>0 (0)</td>
<td>NA</td>
<td>20 (74.1)</td>
<td>NA</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 4. Biomarker data from patients before starting with biological therapies (anti-IL5 and anti-IgE).

<table>
<thead>
<tr>
<th></th>
<th>United Kingdom</th>
<th>Belgium</th>
<th>Spain</th>
<th>Poland</th>
<th>The Netherlands</th>
<th>Hungary</th>
<th>Slovenia</th>
<th>Denmark</th>
<th>Sweden</th>
<th>Germany</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before starting anti-IL5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood eosinophils x10^6 cells/L, median [IQR]</td>
<td>0.403 (0.310-0.509)</td>
<td>0.490 (0.380-0.540)</td>
<td>0.550 (0.405-0.605)</td>
<td>0.490 (0.405-0.509)</td>
<td>0.360 (0.233-0.670)</td>
<td>0.685 (0.280-0.853)</td>
<td>0.210 (0.150-0.438)</td>
<td>0.340 (0.100-0.650)</td>
<td>0.800 (0.075-1.00)</td>
<td>NA</td>
</tr>
<tr>
<td>Serum total IgE IU/ml, median [IQR]</td>
<td>129 (44-424)</td>
<td>270 (90-576)</td>
<td>416 (91-791)</td>
<td>408 (160-791)</td>
<td>140 (48-856)</td>
<td>56 (28-200)</td>
<td>140 (53-255)</td>
<td>164 (58-342)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>FeNO ppb, median [IQR]</td>
<td>24 (8-48)</td>
<td>46 (40-76)</td>
<td>27 (20-47)</td>
<td>36 (24-60)</td>
<td>52 (34-135)</td>
<td>89.5 (55-101)</td>
<td>38 (30-56)</td>
<td>57 (29-80)</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

| Before starting anti-IgE |                |            |           |           |                |         |          |         |        |         |
| Blood eosinophils x10^6 cells/L, median [IQR] | 0.300 (0.100-0.500) | 0.250 (0.166-0.310) | 0.420 (0.200-0.600) | 0.220 (0.010-0.510) | NA | 0.210 (0.150-0.438) | 0.210 (0.150-0.438) | 0.130 (0.100-0.300) | NA | NA |
| Serum total IgE IU/ml, median [IQR] | 326 (159-567) | 238 (107-626) | 243 (114-515) | 154 (74-388) | NA | 172 (118-233) | 118 (52-795) | 148 (92-228) | NA | NA |
| FeNO ppb, median [IQR] | 39 (24-82) | 29 (16-41) | 36 (20-57) | NA | NA | 34 (27-80) | 75 (41-92) | 10 (12-30) | NA | NA |

Data are represented as median with interquartile range from quartile 1 – quartile 3. FeNO: fraction of exhaled Nitric Oxide.
Figure legends

Figure 1. Participating countries in the SHARP Fast Mover Project (FMP).

Figure 2. Inclusion criteria and criteria for preselection of patients in the different registries.

Figure 3. A. Overview of maintenance treatment of patients that start with anti-IL5 biologicals, ICS: Inhalation Corticosteroids, LABA: long-acting beta agonist, LAMA: long-acting muscarinic antagonist, OCS: oral corticosteroids. B. Mean ICS dose, as fluticasone equivalents, in patients that start with anti-IL5 biological therapies. C. Median maintenance OCS dose with interquartile range (Q1-Q3), in prednisone equivalents, in patients that start with anti-IL5 biological therapies. Median values in: UK=10, ES=12.5, NL=10, SL=10, PL=9, HU=10, SE=10, BE=2.5 mg/day.

Figure 4. A. Overview of maintenance treatment of patients that start with anti-IgE biologicals, ICS: Inhalation Corticosteroids, LABA: long-acting beta agonist, LAMA: long-acting muscarinic antagonist, OCS: oral corticosteroids. B. Mean ICS dose, as fluticasone equivalents, in patients that start with anti-IgE biological therapies. C. Median maintenance OCS dose with interquartile range (Q1-Q3), in prednisone equivalents, in patients that start with anti-IgE biological therapies. Median values in: UK=13, ES=10.7, BE=9, PL=7, HU=5 mg/day.
References


