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Early View

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Characteristics and treatment regimens across ERS SHARP severe asthma registries

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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 life style 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 FEV_1 and FVC (% of predicted), patients in the Dutch registry had the best lung function, while those in the Hungarian had the worst lung functions (FEV_1: 76.9% vs. 56.0% and FVC: 98.3% vs. 76.6%). Median blood eosinophil levels varied from 0.230 x 10^9 cells/ml (NL) to 0.800 x 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 $x10^9$ cells/L (DM) to 0.800 $x10^9$ 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 life style 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 FEV_1 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/m^2 and the difference in

average BMI between the UK (30.6 kg/m^2) and Italy (26.2 kg/m^2) 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) FEV_1, but only 9 out of 11 registries also record pre-BD FVC. Information on lung function reversibility is even less common, with post-BD FEV_{-1} currently recorded in only 7 registries. The bigger challenge, however, lies in the harmonization of definitions of variables. The definition for FEV_1 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.

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Tables

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

Country name	Abbreviation
Belgium	BE
Denmark	DM
Germany	DE
Hungary	HU
Italy	IT
Poland	PL
Slovenia	SL
Spain	ES
Sweden	SE
The Netherlands	NL
The United Kingdom	UK

Table 2. Baseline characteristics of patients included in different severe asthma registries that are part of SHARP.

		United Kingdom	Belgium	Italy	Spain	The Netherlands	Germany	Poland	Slovenia	Hungary	Denmark	Sweden
Number of patients, n		765	629	434	410	237	209	193	140	130	59	27
Age, years (SD)		47.6 (14.5)	56.9 (14.7)	54.1 (13.7)	56.4 (14.8)	52.8 (14.2)	44.4 (20.4)	48.4 (14.6)	53.5 (12.8)	58.3 (12.9)	51.9 (16.1)	50 (8.6)
Male, n (%)		285 (37.3)	265 (42.1)	183 (41.9)	133 (32.4)	112 (47.3)	98 (46.9)	76 (39.4)	42 (30)	42 (32.3)	28 (47.5)	14 (51.9)
Smoking status, n (%)	Current	30 (4.1)	60 (9.5)	12 (2.7)	29 (7.1)	2 (0.9)	5 (2.4)	0 (0)	1 (0.7)	8 (6.2)	2 (4.0)	0 (0)
	Never smoker	526 (71.7)	368 (58.5)	352 (80.5)	281 (68.5)	136 (57.9)	125 (59.8)	171 (88.6)	92 (65.7)	108 (83.1)	24 (48.0)	16 (59.3)
	Ex-smoker	178 (24.3)	201(32.0)	73 (16.7)	100 (24.4)	97 (41.3)	79 (37.8)	22 (11.4)	47 (33.5)	14 (10.8)	19 (38.0)	11 (40.7)
Pack-years, median (IQR)		15 (5-20)	15 (6-27)	9 (4-15)	19 (10-23)	10 (4-19)	8 (2-15)	12.5 (15)	10 (3-20)	<5 PY	8.5 (2.2-15)	5 (4-9)
BMI, kg/m^2 (SD)		30.6 (7.4)	27.7 (12.6)	26.2 (5.0)	28.2 (6.0)	28.3 (5.4)	27.4 (10.8)	28.1	27.1 (5.8)	26.9 (5.4)	27.1 (5.4)	27.7 (5.3)
FEV1, %pred (SD)		67.8 (22.8)	67.9 (21.6)	71.4 (20.2)	68.1 (36.1)	76.9 (22.2)	70.3 (23.0)	63.2 (23.5)	69.6 (19.8)	56.0 (16.8)	72.0 (19.1)	66.0 (19.9)
FVC, %pred (SD)		85.3 (19.8)	88.2 (20.2)	88.2 (21.1)	NA	98.3 (20.5)	84.9 (19.7)	NA	95.0 (15.6)	76.6 (18.5)	78.2 (18.3)	86.8 (19.6)
Eosinophils x10^9 cells/L, median (IQR)		0.300 (0.200-0.600)	0.280 (0.225-0.539)	0.540 (0.190-0.645)	0.310 (0.100-0.530)	0.290 (0.105-0.570)	0.230 (0.100-0.580)	0.410 (0.200-0.740)	0.260 (0.120-0.440)	0.345 (0.140-0.578)	0.250 (0.100-0.600)	0.800 (0.600-1.000)
Neutrophils x10^9 cells/L, median (IQR)		NA	NA	4.75 (3.12-5.66)	NA	5.48 (4.09-7.25)	5.02 (3.71-7.15)	NA	5.16 (3.60-6.80)	5.26 (3.98-7.37)	NA	3.80 (2.90-5.10)
Total IgE IU/ml, median (IQR)		165 (55.0-491)	190 (68.0-513)	272 (122-561)	236 (102-516)	144 (49-368)	197 (78.0-579)	167.5 (359)	238 (115-358)	164 (54.7-385)	164 (74.3, 283)	275 (115-820)
FeNO ppb, median (IQR)		41 (23-77)	25 (14-42)	32 (17-64)	33 (19-52)	33 (20-60)	33 (19-79)	27 (27)	66 (27-101)	32 (18-56)	26 (13-49)	57 (29-80)
Adult-onset asthma, n (%)		385 (59.8)	200 (31.8)	105 (24.0)	NA	129 (63.2)	61 (39.4)	68 (35.2)	110 (78)	89 (68.5)	26 (76)	24 (88.9)
ACQ, mean (SD)		3.0 (1.3)	2.5 (1.3)	2.9 (1.5)	NA	2.1 (1.2)	2.6 (1.5)	3.3 (0.9)	NA	NA	2.4 (1.4)	1.8 (1)
ACT, mean (SD)		NA	13.2 (5.4)	17.2 (5 .4)	15.9 (5.8)	NA	15 (6.0)	12.3	16.7 (5.5)	16.6 (1.2)	NA	12 (3.8)
Uncontrolled based on ACQ/ACT, n (%)		581 (84.6)	331 (76.1)	250 (54.6)	221 (68.8)	88 (61.5)	135 (71.1)	191 (99)	87 (64.0)	130 (100)	21 (70)	27 (100)
Hospitalization last year, n (%)		291 (39.5)	229 (36)	53 (17.6)	52 (12.7)	NA	55 (32.4)	78 (40.5)	61 (47.2)	36 (28)	16 (40)	1 (3.7)

Included in, n (%)	Primary care	0 (0)	0 (0)	0 (0)	16 (3.9)	0 (0)	NA	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	Secondary care	0 (0)	52 (8.3)	0 (0)	125 (30.5)	76 (32.1)	NA	0 (0)	0 (0)	44 (33.8)	0 (0)	0 (0)
	Tertiary care	765 (100.0)	577 (91.7)	437 (100)	269 (65.6)	161 (67.9)	NA	193 (100)	139 (100)	86 (66.2)	59 (100)	27 (100)
GINA 4 treatment, n (%)		162 (21.2)	309 (49.0)	18 (5.7)	197 (48.1)	113 (47.7)	130 (62.2)	53 (27.5)	87 (62.6)	93 (71.5)	24 (49.0)	15 (55.6)
GINA 5 treatment, n (%)		569 (74.4)	320 (51.0)	297 (94.3)	210 (51.2)	118 (49.8)	79 (37.8)	140 (72.5)	52 (37.4)	37 (28.5)	14 (28.6)	12 (44.4)
Biological use, n (%)	total	479 (64.5)	160 (25.0)	215 (49.5)	210 (51.2)	82 (34.6)	80 (38.3)	137 (71.0)	66 (47.4)	30 (23.1)	59	0 (0)
	Anti-IgE	115 (25.4)	130 (21.0)	180 (41.2)	197 (48.1)	29 (12.2)	41 (19.6)	129 (66.8)	59 (42.4)	16 (12.3)	18 (30.5)	0 (0)
	Anti-IL5	337 (74.4)	30 (5.0)	35 (8.1)	13 (3.2)	53 (22.4)	39 (18.7)	8 (4.1)	7 (5.0)	14 (10.8)	41 (69.5)	0 (0)
	Anti-IL4/IL13	1 (0.2)	0 (0)	NA	0 (0)	0 (0)	NA	0 (0)	0 (0)	0 (0)	0	0 (0)
Thermoplasty, n (%)		0 (0.0)	9 (1.4)	NA	0 (0)	3 (1.3)	NA	0 (0)	2 (1.4)	0 (0)	0	0 (0)
High altitude treatment, n (%)		NA	0 (0)	NA	0 (0)	33 (14)	NA	0 (0)	0 (0)	0 (0)	NA	0 (0)
ICS* mean dose (SD)		934 (449)	954 (501)	542 (489)	1225 (445)	1027 (737)	676 (398)	1220 (668)	491 (163)	920 (370)	1073 (372)	1196 (641)
OCS[†] Mean dose, median (IQR)		10.0 (10.0-20.0)	9.0 (5.0-10.0)	10.7 (5.0-20.0)	10.0 (5.0-10.0)	10.0 (5.0-17.5)	10.0 (5.0-15.0)	7.0 (7.0-15.0)	10.0 (5.0-10.0)	7.5 (5.0-10.0)	NA	10.0 (7.5-10.0)

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).

Medication use		**United Kingdom**	**Belgium**	**Italy**	**Spain**	**Poland**	**The Netherlands**	**Hungary**	**Slovenia**	**Denmark**	**Sweden**	**Germany**
n		477	469	219	210	193	143	100	73	49	27	NA
GINA step 4, n (%)		152 (31.9)	347 (74)	2 (2.0)	166 (79.0)	53 (27.5)	54 (37.8)	74 (74.0)	42 (57.5))	24 (49)	15 (55.6)	NA
GINA step 5, n (%)		325 (68.1)	109 (23)	98 (98.0)	44 (20.9)	140 (72.5)	87 (60.8)	26 (26.0)	31 (42.4)	14 (29)	12 (44.4)	NA
SABA, n (%)		444 (93.3)	377 (90.2)	4 (4.0)	32 (15.2)	193 (100)	107 (74.8)	100 (100)	43 (58.9)	29 (59.2)	27 (100)	NA
SAMA, n (%)		NA	NA	NA	175 (15.5)	38 (19.7)	25 (17.5)	0 (0)	28 (38.0)	1 (2.0)	8 (29.6)	NA
LABA, n (%)		436 (92.2)	457 (97.4)	219 (100)	206 (97.2)	155 (80.3)	135 (94.4)	100 (100)	72 (98.0)	43 (87.8)	27 (100)	NA
LAMA, n (%)		269 (56.8)	113 (24.1)	40 (40.4)	35 (28.9)	37 (19.2)	42 (29.4)	14 (14)	54 (73.9)	22 (44.9)	8 (30)	NA
ICS, n (%)		477 (100)	457 (97.4)	219 (100)	212 (100)	193 (100)	142 (99.3)	100 (100)	73 (100)	46 (93.9)	27 (100)	NA
ICS mean dose*, µg/day (SD)		973 (508)	986 (479)	570 (497)	1320 (465)	1220 (668)	1178 (797)	909 (386)	700.1 (207.4)	1073 (372)	1196 (641)	NA
LTRA, n (%)		188 (41.6)	251 (55.0)	37 (37.4)	123 (58.6)	128 (66.3)	29 (20.3)	45 (45.0)	30(41.09)	28 (57.1)	21 (77.8)	NA
Theophylline, n (%)		120 (25.3)	65 (14.0)	7 (7.1)	22 (11.2)	52 (26.9)	6 (4.2)	35 (35.0)	1 (1.3)	5 (10.2)	2 (7.4)	NA
OCS maintenance	n (%)	325 (68.1)	102 (22.0)	105 (71.9)	45 (10.3)	87 (45.1)	88 (60.8)	26 (26.0)	31 (42.4)	NA	17 (63.0)	NA
Dose†	DDD (SD)†	NA	NA	NA	1.81 (0.89)	NA	1.4 (1.1)	0.67 (0.34)	NA	NA	0.94 (0.29)	NA
	Median (IQR)	10.0 (10.0-20.0)	10.0 (5.0-10.0)	10.0 (5.0-10.0)	10.0 (5.0-10.0)	7.0 (7.0-15.0)	10.0 (7.5-19.4)	6.9 (3.4-10.0)	10.0 (5.0-12.0)	NA	10.0 (7.5-10.0)	NA
NSAIDS, n (%)		NA	25 (5.0)	NA	NA	44 (22.8)	3 (2.2)	0 (0)	NA	NA	20 (74.1)	NA

Data are represented as mean with standard deviation (SD) unless otherwise specified. IQR: Interquartile range from quartile 1 – quartile 3, GINA: Global Initiative for asthma, SABA: short-acting beta agonist, LAMA: short-acting muscarinic antagonists, LABA: long-acting beta agonists, LAMA: long-acting muscarinic antagonists, ICS: inhalation corticosteroids, LTRA: leukotriene receptor antagonists, OCS: oral corticosteroids, NSAIDS: non-steroidal anti-inflammatory drugs. *: dose expressed as fluticasone equivalents, †: dose expressed as prednisone equivalents.

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

	United Kingdom	Belgium	Spain	Poland	The Netherlands	Hungary	Slovenia	Denmark	Sweden	Germany
Before starting anti-IL5										
Blood eosinophils x10^9 cells/L, median (IQR)	0.400 (0.300-0.700)	0.490 (0.320-0.760)	0.530 (0.330-0.830)	0.450 (0.405-0.855)	0.360 (0.165-0.610)	0.685 (0.233-1.010)	0.440 (0.280-0.670)	0.27 (0.100-0.600)	0.800 (0.600-1.000)	NA
Serum total IgE IU/ml, median (IQR)	129 (44-404)	270 (90-376)	431 (168 - 594)	405 (360-791)	140 (48-366)	56 (29-200)	149 (53-256)	164 (58-342)	275 (115-820)	NA
FeNO ppb, median (IQR)	54 (31-81)	43 (32-48)	48 (40-70)	27 (20-47)	36 (24-60)	52 (34-135)	89.5 (55-101)	38 (30-56)	57 (29-80)	NA
Before starting anti-IgE										
Blood eosinophils x10^9 cells/L, median (IQR)	0.300 (0.100-0.500)	0.250 (0.166-0.310)	0.420 (0.200-0.600)	0.220 (0.100-0.510)	NA	0.210 (0.150-0.438)	0.235 (0.150-0.370)	0.130 (0.100-0.300)	NA	NA
Serum total IgE IU/ml, median (IQR)	324 (139-567)	238 (107-626)	243 (114-515)	154 (74-388)	NA	172 (118-233)	118 (32-795)	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.

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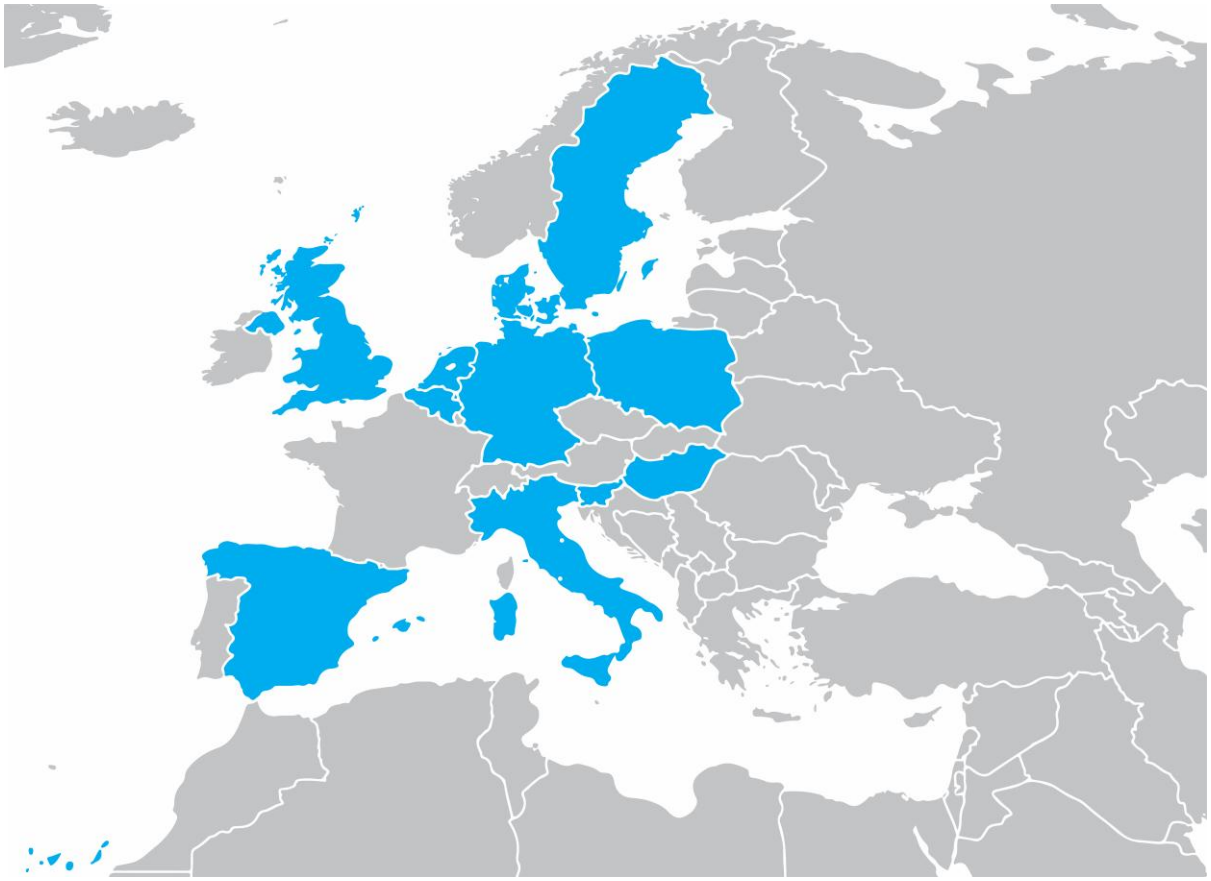
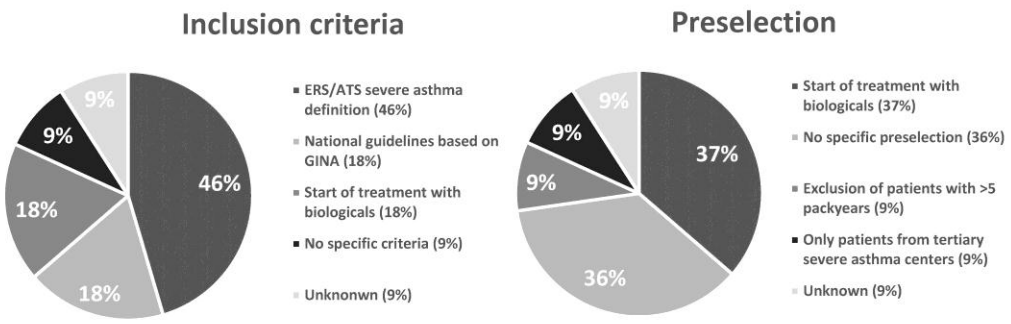
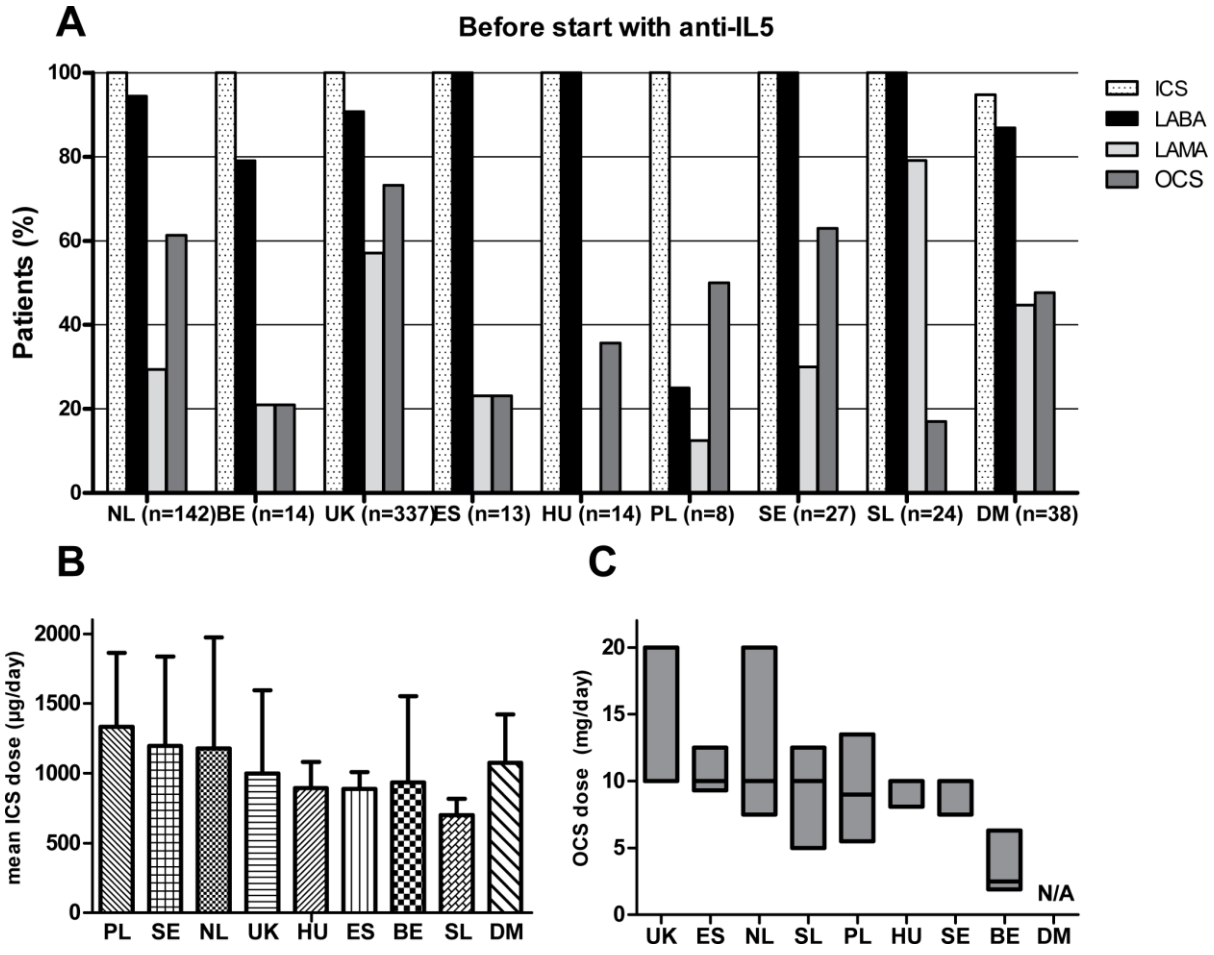
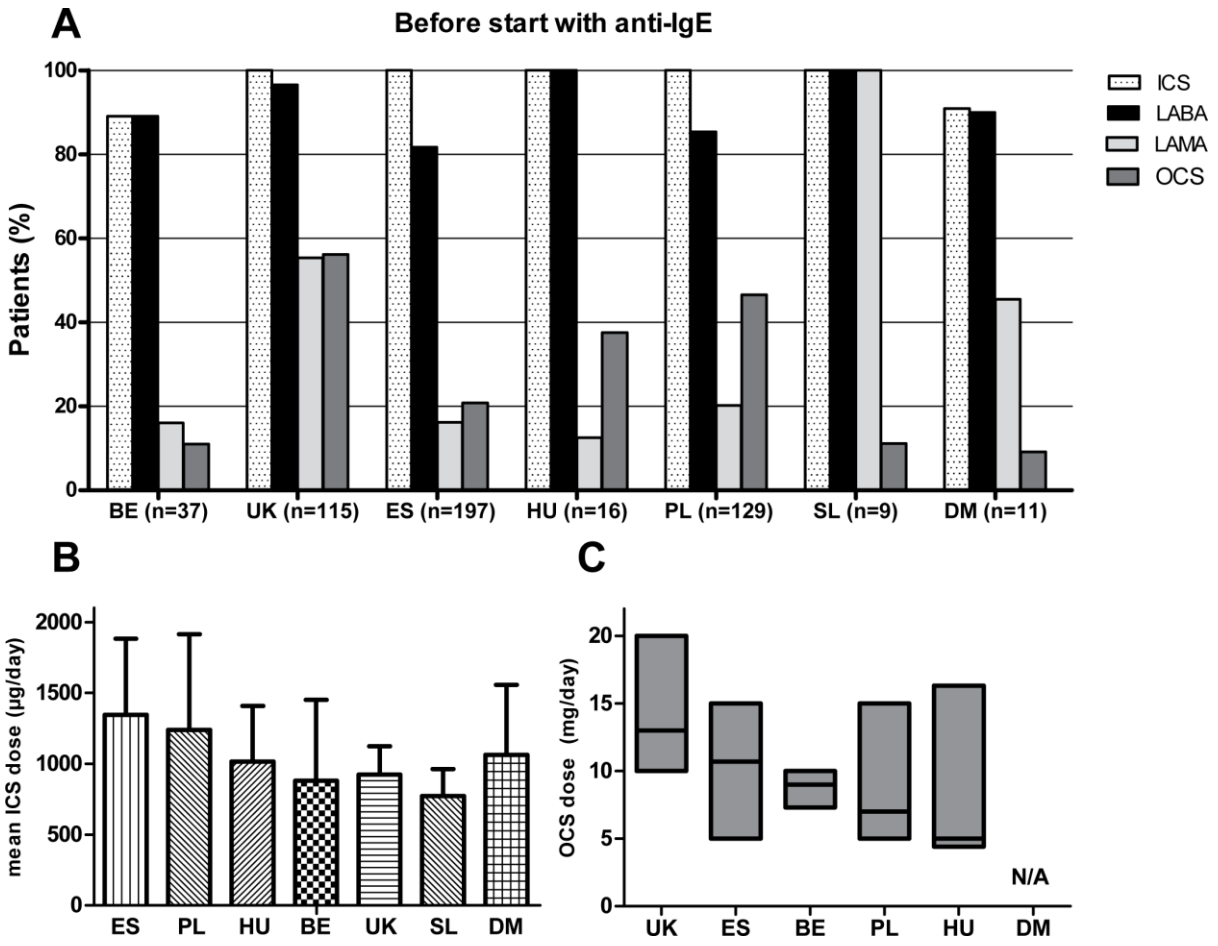



Inclusion criteria
46%
18%
18%
9%
9%
ERS/ATS severe asthma definition (46%)
National guidelines based on GINA (18%)
Start of treatment with biologicals (18%)
No specific criteria (9%)
Unknonwn (9%)
Preselection
37%
36%
9%
9%
9%
Start of treatment with biologicals (37%)
No specific preselection (36%)
Exclusion of patients with >5 packyears (9%)
Only patients from tertiary severe asthma centers (9%)
Unknown (9%)


A
Before start with anti-IL5
Patients (%)
100
80
60
40
20
0
ICS
LABA
LAMA
OCS
NL (n=142)
BE (n=14)
UK (n=337)
ES (n=13)
HU (n=14)
PL (n=8)
SE (n=27)
SL (n=24)
DM (n=38)
B
mean ICS dose (µg/day)
2000
1500
1000
500
0
PL
SE
NL
UK
HU
ES
BE
SL
DM
C
OCS dose (mg/day)
20
15
10
5
0
N/A
UK
ES
NL
SL
PL
HU
SE
BE
DM


A
Before start with anti-IgE
Patients (%)
100
80
60
40
20
0
BE (n=37)
UK (n=115)
ES (n=197)
HU (n=16)
PL (n=129)
SL (n=9)
DM (n=11)
ICS
LABA
LAMA
OCS
B
mean ICS dose (µg/day)
2000
1500
1000
500
0
ES
PL
HU
BE
UK
SL
DM
C
OCS dose (mg/day)
20
15
10
5
0
N/A
UK
ES
BE
PL
HU
DM

Characteristics and treatment regimens across ERS SHARP severe asthma registries

- Supplementary materials -

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Supplementary table 1. Baseline characteristics of patients enrolled in the national SHARP registries involved in the fast mover project.

Parameter		NL	Belgium	United Kingdom	Spain	Hungary	Poland	Sweden	Germany	Italy	Slovenia	Denmark
Demographic												
Age	n	237	629	765	410	130	193	27	209	434	140	59
	years	52,8	56,9	47,6	56,4	58,3	48,4	50	44,4	54,1	53,5	51,9
	SD	14,2	14,7	14,5	14,8	12,9	14,6	8,6	20,4	13,7	12,8	16,1
Male	n	112	265	285	133	42	76	14	98	183	42	28
	%	47,3	42,1	37,3	32,4	32,3	39,4	51,9	46,9	41,9	30	47,5
Smoking status available	n	235	629	734	410	130	193	27	209	437	140	50
Current smoker	n	2	60	30	29	8	0	0	5	12	1	2
	%	0,9	9,5	4,1	7,1	6,2	0	0	2,4	2,7	0,7	4
Never smoker	n	136	368	526	281	108	171	16	125	352	92	24
	%	57,9	58,5	71,7	68,5	83,1	88,6	59,3	59,8	80,5	65,7	48
Ex-smoker	n	97	201	178	100	14	22	11	79	73	47	19
	%	41,3	32	24,3	24,4	10,8	11,4	40,7	37,9	16,7	33,5	38
Pack-years	n	94	194	179	25	22	22	11	85	85	48	16
	years, median	10	15	15	19	<5 PY	NA	5	8	9	10	8,5
	Q1	4	6	5	10	<5 PY	NA	4	2	4	3	2,2
	Q3	19	27	20	23	<5 PY	NA	9	15	15	20	15
Clinical												
BMI	n	236	629	740	410	130	193	27	207	295	138	58
	kg/m^2	28,3	27,7	30,6	28,2	26,9	28,1	27,7	27,4	26,2	27,1	27,1
	SD	5,4	12,6	7,4	6	5,4	4,48	5,3	10,8	5	5,8	5,4
Pre-BD FEV_1	n	234	607	669	87	130	193	27	182	285	140	50
	%pred	76,9	67,9	67,8	68,1	56	63,2	66	70,3	71,4	69,6	72,0
	SD	22,2	21,6	22,8	36,1	16,8	23,5	19,9	23	20,2	19,8	19,4
Pre-BD FVC	n	234	607	647	NA	130	NA	27	182	280	137	49
	%pred	98,3	88,2	85,3	NA	76,6	NA	86,8	84,9	88,2	95	78,2
	SD	20,5	20,2	19,8	NA	18,5	NA	19,6	19,7	21,1	15,6	18,3
Post-BD FEV_1	n	152	629	374	NA	130	NA	27	65	193	NA	NA
	%pred	81	75	73,4	NA	63	NA	73,2	70,2	77,8	NA	NA
	SD	22,3	57,1	22,5	NA	17,5	NA	19	33,2	28,4	NA	NA
Post-BD FVC	n	152	NA	359	NA	130	NA	27	NA	NA	NA	NA
	%pred	102,4	NA	90,7	NA	82,9	NA	91,7	NA	NA	NA	NA
	SD	18	NA	20,1	NA	19,2	NA	14,5	NA	NA	NA	NA
PC20	n	NA	55	12	NA	NA	NA	NA	NA	NA	NA	NA
	mg/ml, median	NA	0,93	14,8	NA	NA	NA	NA	NA	NA	NA	NA
	Q1	NA	0,26	4	NA	NA	NA	NA	NA	NA	NA	NA
	Q3	NA	7,66	16	NA	NA	NA	NA	NA	NA	NA	NA
KCO	n	97	482	491	NA	16	NA	27	76	NA	49	NA
	%pred (SD)	98,2	97,3	97,3	NA	85,8	NA	79,3	76,7	NA	83,4	NA

	SD	18,8	20,9	38,9	NA	4,1	NA	15,9	21	NA	20,5	NA
Medical history available	n	204	629	644	410	130	193	27	170	301	140	33
Adult onset	n	129	200	385	NA	89	68	24	61	105	110	26
	%	63,2	31,8	59,8	NA	68,5	35,2	88,9	39,4	24	78	76,0
Asthma hospitalization during past 12 months	n	NA	229	291	52	36	78	1	55	53	61	16
	%	NA	36	39,5	12,7	28	40,5	3,7	32,4	17,6	47,2	40,0
Ever near fatal exacerbations	n	31	76	NA	0	11	52	2	16	10	21	0
	%	13,1	12	NA	0	8	27	7,4	9,4	3,3	16,1	0
ACQ	n	143	439	687	NA	NA	193	17	190	192	NA	33
	mean score	2,1	2,5	3	NA	NA	3,3	1,8	2,6	2,9	NA	2,4
	SD	1,2	1,3	1,3	NA	NA	0,9	1	1,5	1,5	NA	1,4
ACT	n	NA	455	NA	327	130	28	10	196	266	136	NA
	mean score	NA	13,2	NA	15,9	16,6	12,3	12	15	17,2	16,7	NA
	SD	NA	5,4	NA	5,8	1,2		3,8	6	5,4	5,5	NA
Uncontrolled asthma (based on ACQ/ACT score)	n	88	331	581	221	130	191	27	135	250	87	21
	%	61,5	76,1	84,6	68,8	100	99	100	71,1	54,6	64	70,0
Lab												
Leukocytes	n	232	NA	NA	NA	125	193	27	114	184	135	NA
	$x10^9$ cells/L (SD)	9,1	NA	NA	NA	9,1	8,4	8,2	8,5	8,5	8,8	NA
	SD	2,8	NA	NA	NA	2,8	2,7	2,9	2,8	4,6	3,3	NA
Eosinophils absolute	n	225	516	749	199	125	193	27	111	228	132	45
	$x10^9$ cells/L (median)	0,290	0,280	0,300	0,310	0,345	0,410	0,800	0,230	0,540	0,260	0,250
	Q1	0,105	0,114	0,200	0,100	0,140	0,200	0,600	0,100	0,190	0,120	0,100
	Q3	0,570	0,539	0,600	0,530	0,578	0,740	1,000	0,580	0,645	0,440	0,600
Eosinophils relative	n	32	517	NA	NA	125	193	27	NA	201	134	NA
	% (SD)	5,2	7,3	NA	NA	4,6	4,7	11,2	NA	6,2	4,1	NA
	SD	9,1	55,9	NA	NA	3,9	4,6	5,7	NA	5,6	3,5	NA
Neutrophils absolute	n	222	NA	NA	NA	125	NA	27	100	183	134	NA
	$x10^9$ cells/L (median)	5,48	NA	NA	NA	5,26	NA	3,80	5,02	4,75	5,16	NA
	Q1	4,09	NA	NA	NA	3,98	NA	2,90	3,71	3,12	3,60	NA
	Q3	7,25	NA	NA	NA	7,37	NA	5,10	7,15	5,66	6,80	NA
Neutrophils relative	n	27	NA	NA	NA	125	NA	27	100	134	132	NA
	% (SD)	65,2	NA	NA	NA	65,2	NA	52,2	62,7	52,4	62,7	NA
	SD	12,7	NA	NA	NA	12,1	NA	8,8	14,5	16,9	1,6	NA
Total IgE (serum)	n	222	533	739	199	65	193	20	66	260	139	36
	IU/ml, median (IQR)	144	190	165	236	164	168	275	197	272	238	164
	Q1	49	68	55	102	54,7	78	115	78	122	115	74
	Q3	368	513	491	516	385	435	820	579	561	358	283
Positive for Aspergillus	n (%)	29	NA	NA	2	0	0	1	28 (molds)	24	NA	NA
	%	12,4	NA	NA	0,5	0	0	3,7	13,9	5,5	NA	NA
Negative for Aspergillus	n (%)	103	NA	NA	NA	40	10	26	28	NA	NA	NA
	%	44	NA	NA	NA	30,7	5,2	96,3	13,9	NA	NA	NA

No Aspergillus result available	n (%)	102	NA	NA	NA	90	183	0	174	NA	NA	NA
	%	43,6	NA	NA	NA	69,2	94,8	0	86,1	NA	NA	NA
FeNO	n	213	450	540	85	69	8	26	7	132	122	50
	ppm, median (IQR)	33	25	41	33	32	27	57	33	32	66	26
	Q1	20	14	23	19	18	20	29	19	17	27	13
	Q3	60	42	77	52	56	47	80	79	64	101	49
Comorbidities												
Comorbidity data available	n	236	622	765	121	130	193	27	201	162-298	139	NA
Aspirin intolerance	n (%)	38	49	NA	72	52	44	7	43	57	33	NA
	%	16,1	8,2	NA	17,6	40	22,8	26,9	21,4	19,1	23,7	NA
Churg-Strauβ syndrome (EGPA)	n (%)	6	18	NA	3	9	2	0	3	NA	4	NA
	%	2,5	3,1	NA	2,5	6,9	1	0	1,5	NA	2,8	NA
ABPA	n (%)	3	24	NA	1	0	0	0	1	NA	3	NA
	%	1,3	3,9	NA	0,8	0	0	0	0,5	NA	2,1	NA
Nasal Polyps	n (%)	107	151	102	295	58	24	9	NA	69	9	NA
	%	45,3	24,3	13,3	72	44,6	12,4	33	NA	42,6	6,4	NA
Bronchiectasis	n (%)	36	104	35	10	2	4	0	10	44	8	NA
	%	15,3	16,7	4,6	2,4	1,5	2,1	0	5	16,5	5,7	NA
Therapy											**SI**	
Therapy data available	n	237	629	765	379	130	193	27	202	437	139	NA
Included in primary care center	n	0	0	0	16	0	0	0	NA	0	0	NA
	%	0	0	0	3,9	0	0	0	NA	0	0	NA
Included in secondary care center	n	76	52	0	125	44	0	0	NA	0	0	NA
	%	32,1	8,3	0	30,5	33,8	0	0	NA	0	0	NA
Included in tertiary care center	n	161	577	765	269	86	193	27	NA	437	139	NA
	%	67,9	91,7	100	65,6	66,2	100	100	NA	100	100	NA
Medication use data available	n	237	629	743	379	130	193	27	209	315	139	NA
GINA step 4 treatment	n	113	308	162	197	93	53	15	130	18	87	NA
	%	47,7	49	21,2	48,1	71,5	27,5	55,6	62,2	5,7	62,6	NA
GINA step 5 treatment	n	118	261	569	210	37	140	12	79	297	52	NA
	%	49,8	41,5	74,4	51,2	28,5	72,5	44,4	37,8	94,3	37,4	NA
Data on adherence is available	n	6	629	603	394	14	193	27	NA	NA	NA	NA
Adherence to therapy is checked	n	6	629	519	332	14	193	27	NA	NA	NA	NA
	%	2,5	100	86,1	84,3	10,8	100	100	NA	NA	NA	NA
On biological treatment	n	82	185	479	210	30	137	0	80	215	66	NA
	%	34,6	29,4	64,5	51,2	23,1	71	0	38,3	49,5	47,4	NA
Anti-IgE	n	29	157	115	197	16	129	0	41	180	59	NA
	%	12,2	25	25,4	48,1	12,3	66,8	0	19,6	41,2	42,4	NA
Anti-IL5	n	53	28	337	13	14	8	0	39	35	7	NA
	%	22,4	4,5	74,4	3,2	10,8	4,1	0	18,7	8,1	5	NA
Anti-IL4/IL13	n	0	0	1	0	0	0	0	NA	NA	0	NA
	%	0	0	0,2	0	0	0	0	NA	NA	0	NA

Received thermoplasty	n	3	9	0	0	0	0	0	NA	NA	2	NA
	%	1,3	1,4	0	0	0	0	0	NA	NA	1,4	NA
Received high altitude treatment	n	33	0	NA	0	0	0	0	NA	NA	0	NA
	%	14	0	NA	0	0	0	0	NA	NA	0	NA
ICS mean fluticasone equivalent	n	234	627	654	251	130	193	27	198	299	138	NA
	µg/day (SD)	1027	954	934	1225	920	1220	1196	676	542	491	NA
	SD	737	501	449	445	370	668	641	398	489	163	NA
OCS maintenance, mean	n	119	137	415	146	37	87	17	79	199	52	NA
	mg/day (median)	10,0	9,0	10,0	10,0	7,5	7,0	10,0	10,0	10,7	10,0	NA
	Q1	5,0	5,0	10,0	5,0	5,0	7,0	7,5	5,0	5,0	5,0	NA
	Q3	17,5	10,0	20,0	10,0	10,0	15,0	10,0	15,0	20,0	10,0	NA

SD: standard deviation, IQR: Interquartile range from quartile 1 – quartile 3, BMI: body mass index, FEV1: Forced expiratory volume in one second, FVC: Forced vital capacity, BD: Broncho-dilator, PC20: provocative concentration causing a 20% drop in FEV1, KCO: Carbon monoxide diffusion, 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.

Supplementary table 2. Baseline characteristics of patients enrolled in the national SHARP registries involved in the fast mover project.

Parameter		**NL**	**Belgium**	**United Kingdom**	**Spain**	**Hungary**	**Poland**	**Sweden**	**Germany**	**Italy**	**Slovenia**	**Denmark**
Demographic												
Age	n	143	471	479	212	100	193	27	NA	219	74	56
	years	55,5	57	48,6	57,9	61	48,4	50	NA	55,1	54,8	53,1
	SD	13,1	14	14,1	13,7	12,7	14,6	8,6	NA	13,8	12,2	15,6
Male	n	81	184	196	76	37	76	14	NA	95	19	26
	%	56,6	39,1	40,9	35,8	37	39,4	51,9	NA	42,8	25,6	46,4
Smoking status available	n	143	471	458	212	100	193	27	NA	219	74	47
Current smoker	n	0	49	6	8	7	0	0	NA	5	1	2
	%	0	10,4	1,3	3,8	7	0	0	NA	2,3	1,3	4,3
Never smoker	n	81	273	343	153	80	171	16	NA	186	47	22
	%	56,6	58	74,9	72,2	80	88,6	59,3	NA	84,9	63,5	46,8
Ex-smoker	n	62	149	109	50	13	22	11	NA	31	26	18
	%	43,4	31,6	23,8	23,6	13	11,4	40,7	NA	14,1	35,1	38,3
Pack-years	n	62	199	97	12	20	22	11	NA	36	27	15
	years, median	10	15	15	20	<5	NA	5	NA	8	10	10
	Q1	4	6	8	5	<5	NA	4	NA	7	2	4
	Q3	20	30	20	25	<5	NA	9	NA	15	22	15
Clinical												
BMI	n	143	471	466	212	100	193	27	NA	95	74	55
	kg/m^2	28,3	27,8	30,6	27,8	27	28,2	27,7	NA	26,5	27,4	27,3
	SD	5,2	14,5	6,6	5,6	5,3	4,48	5,3	NA	5,3	6,3	5,4
Pre-BD FEV_1	n	142	456	421	26	100	193	27	NA	98	74	48

	%pred	75,7	67,8	65,2	63,9	56	63,2	66	NA	74,2	64,9	71,8
	SD	23,4	22,3	21,8	21,4	16,8	23,5	19,9	NA	20,6	18,9	19,3
Pre-BD FVC	n	142	456	408	NA	100	NA	27	NA	96	71	47
	%pred	96,5	87,9	85,1	NA	76,2	NA	86,8	NA	90,6	93,2	78,1
	SD	21,2	20,8	19,7	NA	19	NA	19,6	NA	20,7	15,4	18,5
Post-BD FEV_1	n	107	471	221	NA	100	NA	27	NA	60	NA	NA
	%pred	80,3	73,5	71,5	NA	61,5	NA	73,2	NA	73,4	NA	NA
	SD	23,1	29,4	22,7	NA	17,5	NA	19	NA	24,8	NA	NA
Post-BD FVC	n	107	NA	209	NA	100	NA	27	NA	NA	NA	NA
	%pred	101,8	NA	90,8	NA	81,3	NA	91,7	NA	NA	NA	NA
	SD	17,4	NA	20,4	NA	19	NA	14,5	NA	NA	NA	NA
PC20	n	NA	48	2	NA	NA	NA	NA	NA	NA	NA	NA
	mg/ml, median	NA	1,1	13,3	NA	NA	NA	NA	NA	NA	NA	NA
	Q1	NA	0,3	3,6	NA	NA	NA	NA	NA	NA	NA	NA
	Q3	NA	8	23	NA	NA	NA	NA	NA	NA	NA	NA
KCO	n	74	374	312	NA	12	NA	27	NA	NA	22	NA
	%pred (SD)	97,5	97,5	98,8	NA	86,3	NA	79,3	NA	NA	84,4	NA
	SD	17,8	20,4	47,1	NA	4,6	NA	15,9	NA	NA	14,8	NA
Medical history available	n	120-137	471	400	212	100	193	27	NA	97-158	74	32
Adult onset	n	85	155	246	NA	72	68	24	NA	49	60	26
	%	70,8	32,9	61,5	NA	72	35,2	88,9	NA	22,4	81,1	81,2
Asthma hospitalization during past 12 months	n	NA	170	180	193	27	78	1	NA	19	33	NA
	%	NA	36,1	38,9	91	27	40,5	3,7	NA	19	47,8	NA
Ever near fatal exacerbations	n	21	50	NA	0	8	52	2	NA	3	13	0
	%	14,7	10,6	NA	0	8	26,9	7,4	NA	3	18,8	0
ACQ	n	90	330	436	NA	NA	193	17	NA	74	NA	30
	mean score	2,3	2,6	2,9	NA	NA	3,3	1,8	NA	2,6	NA	2,4
	SD	1,3	1,3	1,4	NA	NA	0,9	1	NA	1,4	NA	1,4
ACT	n	NA	345	NA	150	100	28	10	NA	84	70	NA
	mean score	NA	12,6	NA	14,9	16,7	12,3	12	NA	16,4	15,8	NA
	SD	NA	5,1	NA	5,4	1,2		3,8	NA	5,5	5,1	NA
Uncontrolled asthma (based on ACQ/ACT score)	n	88	261	363	114	100	191	27	NA	96	53	21
	%	96,7	79,1	83,3	76	100	99	100	NA	60,8	75,3	70,0
Lab												
Leukocytes	n	142	NA	NA	NA	97	193	27	NA	67	72	NA
	$x10^9$ cells/L (SD)	9	NA	NA	NA	9,07	8,4	8,24	NA	8,46	9,2	NA
	SD	2,3	NA	NA	NA	2,77	2,7	2,9	NA	3,62	3,62	NA
Eosinophils absolute	n	141	388	474	125	97	193	27	NA	75	72	45
	$x10^9$ cells/L (median)	0,360	0,260	0,400	0,600	0,325	0,410	0,800	NA	0,660	0,280	0,250
	Q1	0,165	0,111	0,200	0,150	0,120	0,200	0,600	NA	0,200	0,140	0,100
	Q3	0,610	0,500	0,600	0,600	0,548	0,740	1,000	NA	0,750	0,460	0,600
Eosinophils relative	n	4	389	NA	NA	97	193	27	NA	74	72	NA

	% (SD)	20,7	8,1	NA	NA	4,2	4,7	11,2	NA	6,9	4,2	NA
	SD	18,1	65,6	NA	NA	3,5	4,6	5,7	NA	5,9	3,3	NA
Neutrophils absolute	n	141	NA	NA	NA	97	NA	27	NA	41	72	NA
	$x10^9$ cells/L (median)	5,46	NA	NA	NA	5,25	NA	3,80	NA	4,80	5,60	NA
	Q1	4,16	NA	NA	NA	3,90	NA	2,90	NA	3,44	3,70	NA
	Q3	7,23	NA	NA	NA	7,48	NA	5,10	NA	5,08	7,50	NA
Neutrophils relative	n	NA	NA	NA	NA	97	NA	27	NA	33	72	NA
	% (SD)	NA	NA	NA	NA	65,1	NA	52,2	NA	54,7	62,7	NA
	SD	NA	NA	NA	NA	12,3	NA	8,8	NA	15,6	12,1	NA
Total IgE (serum)	n	141	403	467	58	39	193	20	NA	71	52	36
	IU/ml, median (IQR)	144	147	172	250	181	168	275	NA	159	149	164
	Q1	49	51	58	117	41	78	115	NA	83	204	74
	Q3	379	453	467	520	445	435	820	NA	392	271	283
Positive for Aspergillus	n (%)	16	NA	NA	0	0	0	1	NA	6	NA	NA
	%	11,2	NA	NA	0	0	0	3,7	NA	6	NA	NA
Negative for Aspergillus	n (%)	64	NA	NA	212	28	10	26	NA	NA	NA	NA
	%	44,8	NA	NA	100	28	5,2	96,3	NA	NA	NA	NA
No Aspergillus result available	n (%)	63	NA	NA	0	72	183	0	NA	NA	NA	NA
	%	44,1	NA	NA	0	72	94,8	0	NA	NA	NA	NA
FeNO	n	125	365	293	58	60	8	26	NA	58	66	48
	ppm, median (IQR)	36	25	50	37	32	27	57	NA	34	63	27
	Q1	24	14	28	21	18	20	29	NA	21	31	14
	Q3	60	42	81	62	54	47	80	NA	67	101	52
Comorbidities												
Comorbidity data available	n	143	445	479	43	100	193	27	NA	49-98	73	NA
Aspirin intolerance	n (%)	25	40	NA	49	40	44	7	NA	16	19	NA
	%	17,5	8,9	NA	23,1	40	22,8	25,9	NA	16,7	26	NA
Churg-Strauβ syndrome (EGPA)	n (%)	4	10	NA	3	6	2	0	NA	NA	4	NA
	%	2,8	2,3	NA	1,4	6	1	0	NA	NA	5,4	NA
ABPA	n (%)	1	18	NA	1	0	0	0	NA	NA	2	NA
	%	0,7	4	NA	0,5	0	0	0	NA	NA	2,7	NA
Nasal Polyps	n (%)	75	113	70	163	48	24	9	NA	26	4	NA
	%	52,4	25,4	14,6	76,9	48	12,4	33	NA	53,1	10,8	NA
Bronchiectasis	n (%)	21	83	27	10	2	4	0	NA	20	6	NA
	%	14,7	18,7	5,6	4,7	2	2,1	0	NA	20,4	8,2	NA

SD: standard deviation, IQR: Interquartile range from quartile 1 – quartile 3, BMI: body mass index, FEV1: Forced expiratory volume in one second, FVC: Forced vital capacity, BD: Broncho-dilator, PC20: provocative concentration causing a 20% drop in FEV1, KCO: Carbon monoxide diffusion, FeNO: fraction of exhaled Nitric Oxide, ACQ: asthma control questionnaire, ACT: asthma control test, GINA: Global Initiative for asthma.

Supplementary table 3. Medication use and biomarker data from patients that are starting with anti-IL5 therapy (mepolizumab, reslizumab, benralizumab).

Medication use		NL	Belgium	United Kingdom	Spain	Hungary	Poland	Sweden	Germany	Italy	Slovenia	Denmark
Medication data available	n	142	12	337	13	14	8	27	NA	NA	24	38
Treatment according to GINA guidelines												
GINA step 4	n	50	7	90	10	9	0	15	NA	NA	7	NA
	%	36,5	58,3	26,8	76,9	64,3	0	55,6	NA	NA	29,2	NA
GINA step 5	n	85	3	246	3	5	4	12	NA	NA	17	NA
	%	62	25	73,2	23,1	35,7	50	44,4	NA	NA	70,8	NA
Medication use												
SABA	n	107	10	315	6	14	8	27	NA	NA	17	21
	%	74,8	83,3	94	46,2	100	100	100	NA	NA	70,8	55,3
SAMA	n	25	NA	NA	5	0	1	8	NA	NA	5	4
	%	17,5	NA	NA	38,5	0	12,5	29,6	NA	NA	20,8	10,5
LABA	n	135	9	302	13	14	2	27	NA	NA	24	33
	%	94,4	75	90,7	100	100	25	100	NA	NA	100	86,8
LAMA	n	42	6	190	3	0	1	8	NA	NA	19	17
	%	29,4	50	57,1	23,1	0	12,5	30	NA	NA	79,1	44,7
ICS	n	142	12	337	13	14	8	27	NA	NA	24	36
	%	100	100	100	100	100	100	100	NA	NA	100	94,7
Mean fluticasone equivalent	n	142	12	283	4	14	8	27	NA	NA	24	33
	µg	1178	935	998	888	893	1335	1196	NA	NA	700	1076
	SD	797	618	597	121	189	529	641	NA	NA	118	345
Leukotriene receptor antagonists	n	29	8	135	10	10	5	21	NA	NA	15	24
	%	20,4	66,7	41,5	76,9	71,4	62,5	77,8	NA	NA	62,5	63,2
Theophylline	n	6	0	84	0	6	3	2	NA	NA	0	5
	%	4,2	0	25,2	0	42,9	37,5	7,4	NA	NA	0	13,2
OCS	n	87	2	246	3	5	4	17	NA	NA	17	18
	%	61,3	16,7	73,2	23,1	35,7	50	63	NA	NA	70,8	47,4
Maintenance treatment, prednisone eq. Dose	n	87	2	246	4	5	4	17	NA	NA	17	NA
	DDD [†]	1,4	NA	NA	1,54	0,95	NA	0,94	NA	NA	NA	NA
	SD	1,1	NA	NA	1,43	0,11	NA	0,29	NA	NA	NA	NA
	Mg/day (median)	10,0	2,5	10,0	12,5	10,0	9,0	10,0	NA	NA	10,0	NA
	Q1	7,5	1,9	10,0	9,3	8,1	5,5	7,5	NA	NA	5,0	NA
	Q3	20,0	6,3	20,0	10,0	10,0	13,5	10,0	NA	NA	12,5	NA
NSAIDS	n	3	1	NA	NA	0	2	20	NA	NA	NA	NA
	%	2,1	8,3	NA	NA	0	25	74,1	NA	NA	NA	NA
Biomarkers												
IgE	n	140	6	331	10	10	8	20	NA	NA	15	28
	Iu/ml, median (IQR)	140	165	129	431	56	405	275	NA	NA	149	164
	Q1	48	154	44	168	29	360	115	NA	NA	53	58

	Q3	366	217	404	594	200	791	820	NA	NA	256	342
Blood eosinophils, absolute	n	141	9	336	12	14	8	27	NA	NA	23	37
	$x10^9$ cells/l (median)	0,360	0,490	0,400	0,530	0,685	0,565	0,800	NA	NA	0,440	0,270
	Q1	0,165	0,320	0,300	0,330	0,233	0,405	0,600	NA	NA	0,280	0,100
	Q3	0,610	0,760	0,700	0,830	1,010	0,855	1,000	NA	NA	0,670	0,600
FeNO	n	125	5	192	11	3	8	26	NA	NA	24	38
	ppm, median (IQR)	36	27	54	48	52	27	57	NA	NA	90	38
	Q1	24	26	31	40	34	20	29	NA	NA	55	30
	Q3	60	62	81	70	135	47	80	NA	NA	101	56

SD: standard deviation, IQR: Interquartile range from quartile 1 – quartile 3, GINA: Global Initiative for asthma, SABA: short-acting beta agonist, LAMA: short-acting muscarinic antagonists, LABA: long-acting beta agonists, LAMA: long-acting muscarinic antagonists, ICS: inhalation corticosteroids, LTRA: leukotriene receptor antagonists, OCS: oral corticosteroids, NSAIDS: non-steroidal anti-inflammatory drugs, FeNO: fraction of exhaled nitric oxide. *: dose expressed as fluticasone equivalents, †: dose expressed as prednisone equivalents.

Supplementary table 4. Medication use and biomarker data from patients that are starting with anti-IgE therapy (omalizumab).

Medication use		**NL**	**Belgium**	**UK**	**Spain**	**Hungary**	**Poland**	**Sweden**	**Germany**	**Italy**	**Slovenia**	**Denmark**
Medication data available	n	NA	87	115	197	16	129	NA	NA	NA	9	11
Treatment according to GINA guidelines												
GINA step 4	n	NA	23	50	156	10	69	NA	NA	NA	8	NA
	%	NA	26,4	43,9	79,2	62,5	53,5	NA	NA	NA	88,9	NA
GINA step 5	n	NA	56	64	41	6	60	NA	NA	NA	1	NA
	%	NA	64,4	56,1	20,8	37,5	46,5	NA	NA	NA	11,1	NA
Medication use												
SABA	n	NA	75	107	16	16	129	NA	NA	NA	5	8
	%	NA	86,2	93,9	8,1	100	100	NA	NA	NA	55,5	72,7
SAMA	n	NA	NA	NA	169	0	26	NA	NA	NA	4	0
	%	NA	NA	NA	85,8	0	20,2	NA	NA	NA	44,4	0
LABA	n	NA	88	109	161	16	110	NA	NA	NA	9	10
	%	NA	100	96,5	81,7	100	85,3	NA	NA	NA	100	90
LAMA	n	NA	18	63	32	2	26	NA	NA	NA	9	5
	%	NA	20,7	55,3	16,2	12,5	20,2	NA	NA	NA	100	45,5
ICS	n	NA	84	115	197	16	129	NA	NA	NA	9	10
	%	NA	96,6	100	100	100	100	NA	NA	NA	100	90,9
Mean fluticasone equivalent	n	NA	84	107	197	16	129	NA	NA	NA	9	8
	µg	NA	881	923	1344	1016	1239	NA	NA	NA	772	1063
	SD	NA	571	201	540	392	677	NA	NA	NA	191	496
Leukotriene receptor antagonists	n	NA	54	46	113	12	86	NA	NA	NA	4	4
	%	NA	62,1	43,8	57,4	75	66,7	NA	NA	NA	44	36,4
Theophylline	n	NA	9	31	22	4	34	NA	NA	NA	0	0
	%	NA	10,3	27,2	11,2	25	26,4	NA	NA	NA	0	0

OCS	n	NA	10	64	41	6	60	NA	NA	NA	1	1
	%	NA	11,5	56,1	20,8	37,5	46,5	NA	NA	NA	11,1	9,1
Maintenance treatment, prednisone eq. Dose	n	NA	4	64	44	6	60	NA	NA	NA	1	NA
	DDD †	NA	NA	NA	1,86	0,88	NA	NA	NA	NA	NA	NA
	SD	NA	NA	NA	0,81	0,7	NA	NA	NA	NA	NA	NA
	Mg/day (median)	NA	9,0	13,0	10,7	5,0	7,0	NA	NA	NA	7,5	NA
	Q1	NA	7,3	10,0	5,0	4,4	5,0	NA	NA	NA	NA	NA
	Q3	NA	10,0	20,0	15,0	16,3	15,0	NA	NA	NA	NA	NA
NSAIDS	n	NA	5	NA	NA	0	27	NA	NA	NA	NA	NA
	%	NA	5,7	NA	NA	0	20,9	NA	NA	NA	NA	NA
Biomarkers												
IgE	n	NA	69	110	177	16	129	NA	NA	NA	5	8
	Iu/ml, median (IQR)	NA	277	324	243	172	154	NA	NA	NA	118	148
	Q1	NA	132	139	114	118	74	NA	NA	NA	32	91,5
	Q3	NA	576	567	515	233	388	NA	NA	NA	795	228,3
Blood eosinophils, absolute	n	NA	31	113	113	14	129	NA	NA	NA	8	8
	$x10^9$ cells/l (median)	NA	0,250	0,300	0,420	0,210	0,220	NA	NA	NA	0,235	0,13
	Q1	NA	0,166	0,100	0,200	0,150	0,100	NA	NA	NA	0,150	0,1
	Q3	NA	0,310	0,500	0,600	0,438	0,510	NA	NA	NA	0,370	0,3
FeNO	n	NA	52	77	47	6	NA	NA	NA	NA	6	10
	ppm, median (IQR)	NA	31	39	36	34	NA	NA	NA	NA	75	10
	Q1	NA	13	24	20	27	NA	NA	NA	NA	40,5	11,8
	Q3	NA	49	82	57	80	NA	NA	NA	NA	92,2	29,8

SD: standard deviation, IQR: Interquartile range from quartile 1 – quartile 3, GINA: Global Initiative for asthma, SABA: short-acting beta agonist, LAMA: short-acting muscarinic antagonists, LABA: long-acting beta agonists, LAMA: long-acting muscarinic antagonists, ICS: inhalation corticosteroids, LTRA: leukotriene receptor antagonists, OCS: oral corticosteroids, NSAIDS: non-steroidal anti-inflammatory drugs, FeNO: fraction of exhaled nitric oxide. *: dose expressed as fluticasone equivalents, †: dose expressed as prednisone equivalents.