Journal of Asthma and Allergy Dovepress

Open Access Full Text Article ORIGINAL RESEARCH

Disease Burden and Access to Biologic Therapy in Patients with Severe Asthma, 2017–2022: An Analysis of the International Severe Asthma Registry

Tham T Le[1], David B Price[2–4], Clement Erhard[5], Bill Cook[6], Anna Quinton[7], Rohit Katial[8], George C Christoff[9], Luis Perez-de-Llano[10], Alan Altraja[11,12], Celine Bergeron[13], Arnaud Bourdin[14], Mariko Siyue Koh[15,16], Lauri Lehtimäki[17,18], Bassam Mahboub[19], Nikolaos G Papadopoulos[20,21], Paul Pfeffer[22,23], Chin Kook Rhee[24], Victoria Carter[2,3], Neil Martin[25,26], Trung N Tran[1] On behalf of the EVEREST Study Working Group

[1]BioPharmaceuticals Medical, AstraZeneca, Gaithersburg, MD, USA; [2]Observational and Pragmatic Research Institute, Singapore; [3]Optimum Patient Care Global, Cambridge, UK; [4]Centre of Academic Primary Care, Division of Applied Health Sciences, University of Aberdeen, Aberdeen, UK; [5]BioPharmaceuticals Medical, AstraZeneca, Cambridge, UK; [6]Respiratory and Immunology, BioPharmaceuticals Medical, AstraZeneca, Gaithersburg, MD, USA; [7]BioPharmaceuticals R&D, AstraZeneca, Cambridge, UK; [8]Global Medical Respiratory, BioPharmaceuticals Medical, AstraZeneca, Gaithersburg, MD, USA; [9]Faculty of Public Health, Medical University Sofia, Sofia, Bulgaria; [10]Department of Respiratory Medicine, University Hospital Lucus Augusti, Lugo, Spain; [11]Department of Pulmonology, University of Tartu, Tartu, Estonia; [12]Lung Clinic, Tartu University Hospital, Tartu, Estonia; [13]Centre for Lung Health, Vancouver General Hospital, University of British Columbia, Vancouver, BC, Canada; [14]PhyMedExp, University of Montpellier, CNRS, INSERM, University Hospital of Montpellier, Montpellier, France; [15]Respiratory and Critical Care Medicine, Singapore General Hospital, Singapore; [16]Duke-NUS Medical School, Singapore; [17]Allergy Centre, Tampere University Hospital, Tampere, Finland; [18]Faculty of Medicine and Health Technology, Tampere University, Tampere, Finland; [19]Rashid Hospital, Dubai Health Authority, Dubai, United Arab Emirates; [20]Division of Infection, Immunity and Respiratory Medicine, University of Manchester, Manchester, UK; [21]Allergy Department, 2nd Pediatric Clinic, University of Athens, Athens, Greece; [22]Department of Respiratory Medicine, Barts Health NHS Trust, London, UK; [23]Barts and the London School of Medicine and Dentistry, Queen Mary University of London, London, UK; [24]Department of Internal Medicine, Division of Pulmonary and Critical Care Medicine, Seoul St. Mary's Hospital, College of Medicine, the Catholic University of Korea, Seoul, South Korea; [25]Respiratory and Immunology, BioPharmaceuticals Medical, AstraZeneca, Cambridge, UK; [26]University of Leicester, Leicester, UK

Correspondence: Trung N Tran, BioPharmaceuticals Medical, Respiratory and Immunology, AstraZeneca, Gaithersburg, MD, USA, Email trung.tran1@astrazeneca.com

Introduction: Patients with severe asthma may be prescribed biologic therapies to improve disease control. The EVEREST study aimed to characterize the global disease burden of patients with severe asthma without access to biologics and those who have access but do not receive biologics, as well as the remaining unmet need despite use of these therapies.

Methods: This was a historical cohort study of patients with severe asthma (aged ≥18 years) in the International Severe Asthma Registry receiving Global Initiative for Asthma (GINA) 2018 step 5 treatment, or with uncontrolled disease at GINA step 4. Prospective data on patient clinical characteristics, healthcare resource utilization, and medication use over a 12-month period between December 2017 and May 2022 were assessed for the following five groups: biologics accessible (omalizumab, mepolizumab, reslizumab, benralizumab, or dupilumab); biologics inaccessible; biologics accessible but not received; biologics accessible and received; and biologic recipients whose asthma remained suboptimally controlled.

Results: Overall, 9587 patients from 21 countries were included. Among patients in the biologics accessible (n=5073), biologics inaccessible (n=3041), and biologics accessible but not received (n=382) groups, 41.4%, 18.7%, and 49.6% experienced at least two exacerbations, 11.5%, 10.5%, and 6.2% required at least one hospitalization, 47.9%, 54.6%, and 71.2% had uncontrolled asthma, and 23.9%, 8.6%, and 11.0% received long-term oral corticosteroids (LTOCS), respectively. Following biologic therapy, among patients who received biologics overall (n=2666) and among those whose asthma remained suboptimally controlled (n=1780), 19.1% and 23.0% experienced at least two exacerbations, 2.7% and 2.9% required at least one hospitalization, and 16.7% and 22.0% received LTOCS, respectively.

Received: 9 March 2024
Accepted: 2 October 2024
Published: 25 October 2024

Conclusion: There is a substantial disease burden in both patients without access to biologics and those with access who do not receive these therapies, although specific outcomes may vary between these groups. There also remains a high unmet need among biologic recipients, many of whom have a suboptimal response to treatment.

Keywords: biologic, disease burden, healthcare resource utilization, severe asthma

Introduction

Asthma is one of the most prevalent chronic respiratory diseases, affecting more than 300 million people worldwide in 2019.[1] An estimated 4–10% of people with asthma have severe asthma,[2–4] which is defined as asthma that remains uncontrolled despite treatment with high-dose inhaled corticosteroids (ICS) plus a long-acting β_2-agonist (LABA; with or without oral corticosteroids [OCS]) and treatment of contributory factors, or asthma that worsens when high-dose treatment is decreased.[5,6] Patients with severe asthma experience frequent asthma exacerbations, leading to hospitalizations, emergency room (ER) visits, and decreased health-related quality of life.[7–9] Consequently, despite the low overall prevalence of severe asthma, these patients account for a disproportionately large share of asthma-related healthcare resource utilization (HCRU) and costs, as well as substantial non-asthma-related HCRU and costs owing to steroid-related adverse events.[7,8]

Several classes of therapy may be given as adjuncts to ICS-LABA to improve disease control in patients with severe asthma, including biologics that target inflammatory molecules and pathways involved in asthma pathogenesis.[5] The landscape of biologic therapy for asthma is rapidly evolving, with new therapies under evaluation and the long-term efficacy and safety of existing therapies becoming more established.[10–12] To date, biologic therapies targeting immunoglobulin E (IgE; omalizumab), interleukin (IL)-5 (mepolizumab, reslizumab), IL-5 receptor (IL-5R; benralizumab), IL-4/13 signaling (dupilumab), and thymic stromal lymphopoietin (tezepelumab), have been shown to be beneficial for patients with severe asthma; these treatments approximately halve rates of exacerbations and hospitalizations while improving lung function, asthma control, and health-related quality of life in randomized controlled trial populations.[13–16] The efficacy of these biologics is generally sustained during long-term use, and rates of adverse events, including those requiring therapy cessation, are low.[11,12] Of the six US Food and Drug Administration-approved biologics for moderate or severe asthma, mepolizumab, reslizumab, benralizumab, and dupilumab have indications for patients with an eosinophilic/type 2 (T2) phenotype,[17–20] omalizumab is indicated for patients with clinically relevant perennial allergen sensitization,[21] and tezepelumab (the most recently approved, in 2021) has no asthma phenotype restriction.[22]

Patients' access to biologic therapies in countries where they are licensed, at least through typical reimbursement processes, requires meeting prescription eligibility criteria (including phenotyping criteria) determined by national and regional regulatory bodies, and usually requires referral to a specialist. Access to biologics therefore varies between countries owing to differences in national healthcare systems regarding reimbursement policies and referral networks.[23] For example, in 2021, one of the eligibility criteria for omalizumab in the United Kingdom (UK) was four or more exacerbations in the previous year, whereas in Estonia and the Netherlands, no exacerbations were required.[23] Regarding referral systems, countries such as Switzerland, Sweden, and Germany have been found to have the lowest barriers to accessing specialists, whereas India had the highest barriers.[24] Previous studies suggest that a significant proportion of patients with severe asthma who meet the eligibility criteria for biologic therapy are not prescribed these agents, although robust data on this topic are lacking.[25–28] Furthermore, approximately 15–50% of patients with severe asthma, including those with nonallergic or non-eosinophilic phenotypes, are not eligible for any of the T2-targeted biologics (omalizumab, mepolizumab, reslizumab, benralizumab, and dupilumab).[25,29–31]

Quantifying the current global clinical and economic burden of patients with severe asthma who lack access to T2-targeted biologic therapy and of patients who have access but do not receive therapy, as well as the remaining unmet need despite use of these biologics, is essential for understanding whether there is still a need for new treatments for patients with severe asthma. Although regional and national severe asthma registries collect valuable country-specific data pertaining to this,[32–34] they typically contain relatively small numbers of patients. A larger data set that can be used to address this knowledge gap is the International Severe Asthma Registry (ISAR),[35,36] a global registry that retrospectively

and prospectively collects standardized, individual-level data from over 17,000 adult patients with severe asthma in 28 countries worldwide at the time of writing.[37]

The EVEREST study aimed to characterize the clinical burden and asthma-related HCRU of patients enrolled in ISAR between December 2017 and May 2022, evaluating patients by their access to biologic therapy in terms of receiving biologics or meeting national prescription eligibility criteria for these therapies.[23] Patients with access to biologic therapy who received it and those who did not receive it were evaluated separately, as were patients with access to biologic therapy whose asthma remained suboptimally controlled despite receiving these therapies.

Materials and Methods

Data Source

ISAR aggregates and standardizes data from existing and newly created severe asthma registries worldwide. Full details regarding asthma diagnostic criteria for ISAR, the definition of severe asthma used, and how data are extracted from registries in participating countries have been published previously.[38] Data from 21 countries were included in this study (Argentina, Australia, Bulgaria, Canada, Colombia, Denmark, Greece, India, Italy, Japan, Korea, Kuwait, Mexico, Poland, Portugal, Saudi Arabia, Spain, Taiwan, United Arab Emirates, UK, and the United States [US]).

The study was designed, implemented, and reported in compliance with the European Network Centres for Pharmacoepidemiology and Pharmacovigilance Code of Conduct (registration number: EUPAS106967) and with all applicable local and international laws and regulations. Registration of the ISAR database with the European Union Electronic Register of Post-Authorization studies was also undertaken (ENCEPP/DSPP/23720). Ethical governance for ISAR was provided by the Anonymised Data Ethics Protocols and Transparency Committee (ADEPT) (approval reference number: ADEPT-1021).[39] All data collection sites in ISAR have obtained regulatory agreement in compliance with specific data transfer laws, country-specific legislation, and relevant ethical boards and organizations. The study was approved by the ISAR International Steering Committee and was performed in accordance with the 1964 Declaration of Helsinki and its later amendments. All participating patients provided informed consent, and their data were anonymized.

Study Design

This was a historical cohort study of patients enrolled in ISAR, using prospective data collected between December 1, 2017, and May 11, 2022. The current analysis included patients who, at enrollment in ISAR, were aged 18 years or older and were receiving Global Initiative for Asthma (GINA; 2018 criteria)[40] step 5 treatment or were receiving step 4 treatment but still had uncontrolled asthma (per GINA 2018[40] or the American Thoracic Society/European Respiratory Society guidelines).[6] Patients who had received bronchial thermoplasty were excluded from the analysis.

The following five groups of patients were studied, with groups 3–5 being subgroups of group 1: 1) biologics accessible; 2) biologics inaccessible; 3) biologics accessible but not received; 4) biologics accessible and received (also referred to herein as biologic recipients); and 5) biologic recipients whose asthma remained suboptimally controlled (also a subgroup of group 4; see Figure 1 for group/subgroup stratification).

The biologics accessible group comprised patients who had been prescribed a biologic that was available during the study period (omalizumab, mepolizumab, reslizumab, benralizumab, or dupilumab; no patients receiving tezepelumab were included because of its recent approval) or who met the prescription criteria for those available biologics from the Biologic Accessibility Score (BACS) system developed by the ISAR group,[23] at any time during the study period. Details of the BACS prescription criteria have been published previously.[23] Briefly, the criteria are specific to each biologic and country, having been based on national regulatory/reimbursement authority criteria in June 2020. They are based on a list of 18 initial criteria: age, weight, asthma phenotype, blood eosinophil count, total serum IgE level, fractional exhaled nitric oxide (FeNO) level, allergic asthma diagnostic requirements (eg, skin prick test), background therapy, biologic history, treatment adherence, OCS use, exacerbation history, asthma control, lung function, symptoms, asthma diagnosis, care manager (eg, severe asthma specialist), and correct inhaler technique.

The biologics inaccessible group comprised patients in the overall cohort who did not meet the criteria for the biologics accessible group above at any time during the study period.

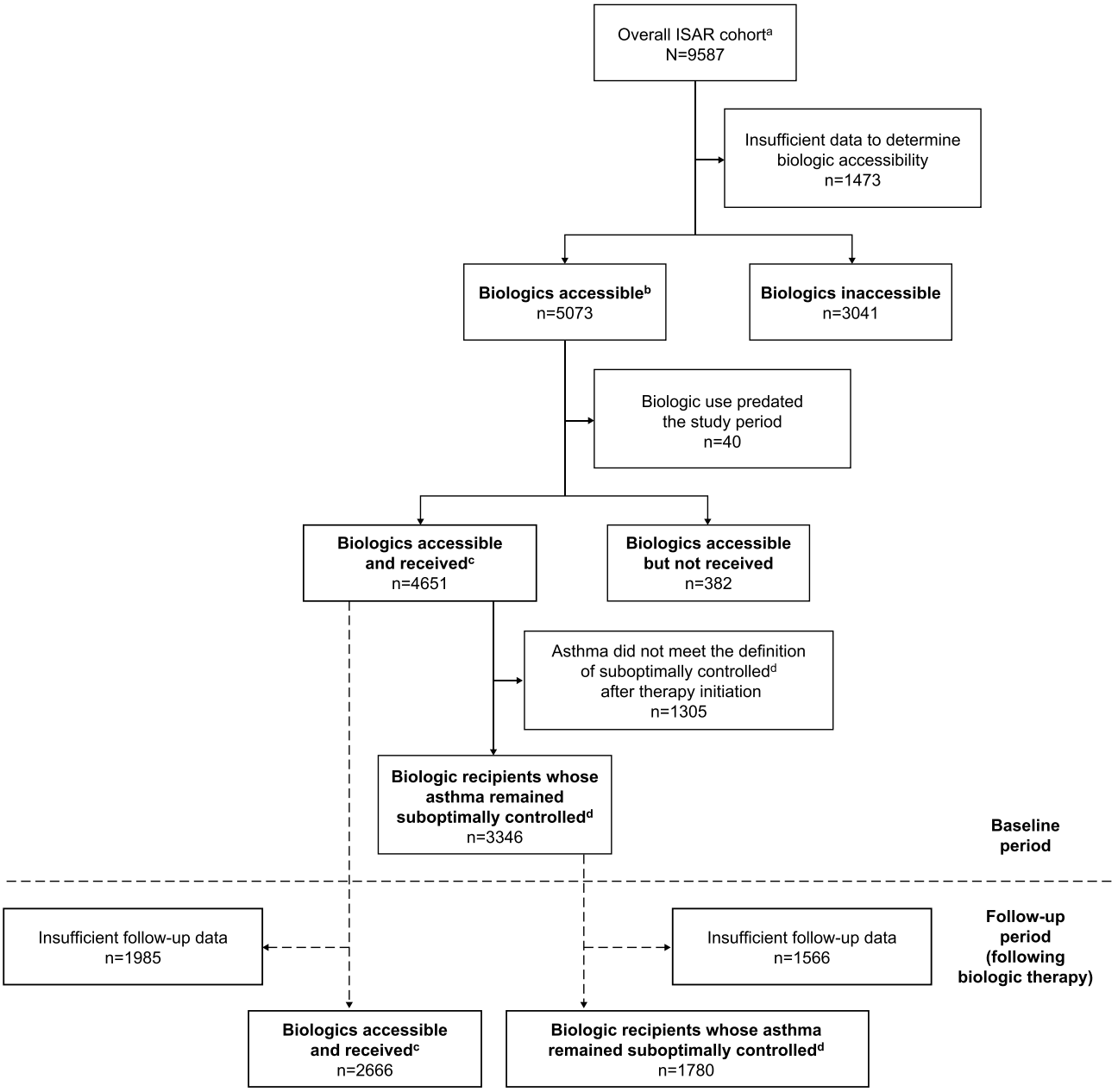

Figure 1 Patient groups evaluated during the baseline period and follow-up period (following biologic therapy).

Notes: [a]The overall cohort included patients aged 18 years or older receiving GINA (2018 criteria) step 5 treatment, or step 4 treatment but had uncontrolled asthma (ERS/ATS criteria).[6] [b]The biologics accessible group comprised patients who either had been prescribed a biologic during the study period (either omalizumab, mepolizumab, reslizumab, benralizumab, or dupilumab) or those who met the prescribing criteria from the BACS.[23] [c]The biologics accessible and received group comprised patients who received at least one dose of biologic therapy for asthma during the study period. [d]The biologic recipients whose asthma remained suboptimally controlled group was defined as patients within the biologics accessible and received group who received at least three doses of a biologic and either had uncontrolled asthma defined by the GINA 2019 criteria[41] following biologic initiation, had a severe exacerbation following biologic initiation, or received LTOCS. This group also included those who had switched or stopped their biologic treatment owing to a reported lack of clinical efficacy.

Abbreviations: ATS, American Thoracic Society; BACS, Biologic Accessibility Score; ERS, European Respiratory Society; GINA, Global Initiative for Asthma; ISAR, International Severe Asthma Registry; LTOCS, long-term oral corticosteroid.

The biologics accessible but not received group comprised patients who met the biologics accessible group criteria above but were not prescribed a biologic therapy during the study period.

The biologics accessible and received group (ie, biologic recipients) comprised patients who met the biologics accessible group criteria and were prescribed an available biologic therapy during the study period.

The biologic recipients whose asthma remained suboptimally controlled group was defined as patients within the biologics accessible and received group who were prescribed at least three doses of a biologic and either had uncontrolled asthma (defined by the GINA 2019 asthma control classification[41]) following biologic initiation, had a severe exacerbation following biologic initiation, or received long-term OCS (LTOCS) treatment. Patients who had switched or stopped their biologic treatment owing to a reported lack of clinical efficacy were also included in this group.

A patient's index date for the study was defined as the closest healthcare professional visit recorded in ISAR to when the patient first met the eligibility criteria for their group during the study period (Supplementary Table 1).

Study Measurements and Variables

Baseline patient demographics and asthma-related clinical characteristics were described for all groups. Patient demographic variables included age, sex, and body mass index. Asthma-related clinical characteristics included smoking status, smoking duration (pack-years), asthma duration, spirometry parameters, biomarker measurements (eg, FeNO level, blood eosinophil count, and serum total IgE level), and the presence of comorbidities.

To assess disease burden at baseline, asthma-related HCRU, asthma control, and medication use during the 12 months preceding the index date (baseline period) were described. Baseline disease burden was described for all groups except biologic recipients whose asthma remained suboptimally controlled, because this group was defined by their response to biologic therapy in the follow-up period. To assess disease burden following receipt of biologic therapy, asthma-related HCRU, asthma control, and medication use were described for the 12 months after the index date (follow-up period) for biologic recipients overall and for those whose asthma remained suboptimally controlled.

Asthma-related HCRU variables included the number of exacerbations, ER visits for asthma, invasive ventilations for severe asthma events, and hospital admissions for asthma. Asthma control was defined as uncontrolled, partly controlled, or well-controlled using the GINA 2019 Asthma Control Criteria/Asthma Control Questionnaire/Asthma Control Test criteria.[41] Use of medications in addition to ICS-LABA, including LTOCS, theophylline, long-acting muscarinic antagonists, and leukotriene receptor antagonists, as well as use of biologics and macrolide antibiotics (including azithromycin), were also evaluated. The reasons for any lack of effectiveness of the biologic therapies received, or any changes in the biologics prescribed, were not assessed. Full details of the study variables are provided in Supplementary Tables 2 and 3.

Statistical Analyses

Descriptive statistics were generated for continuous variables (mean and standard deviation, or median and range) and categorical variables (proportion with 95% confidence intervals, as applicable); no statistical comparisons between groups were made. Missing data were quantified but excluded from the analyses.

Results

Study Population

In total, 9587 patients were included in the study (Figure 1). Of these, 5073 (52.9%) had access to a T2-targeted biologic therapy and 3041 (31.7%) were classed as biologics inaccessible (insufficient data were available to determine biologic accessibility for 1473 patients [15.4%]). Among patients with access to biologics, 4651 (91.7%) received a biologic and 382 (7.5%) did not; 3346 biologic recipients (71.9%) had asthma that remained suboptimally controlled following biologic therapy. Among biologic recipients overall, 2751 (59.1%) received an anti–IL-5 therapy, 1834 (39.4%) received an anti-IgE therapy, 956 (20.6%) received an anti–IL-5R therapy, and 445 (9.6%) received an anti–IL-4/13 therapy (Supplementary Table 4). In total, 2666 biologic recipients overall were included in the follow-up analysis, including 1780 patients whose asthma remained suboptimally controlled following biologic therapy (Figure 1).

Patient Demographics and Clinical Characteristics

The baseline demographics and clinical characteristics of the patient groups are shown in Table 1 (split by biologic class for biologic recipients overall in Supplementary Table 4). Patients were predominantly female (ranging from 63.0% to

Table 1 Baseline Demographics and Clinical Characteristics of Patient Groups

Demographic/ Characteristic	Overall ISAR Cohort (N=9587)				
	Biologics Accessible (n=5073)	Biologics Inaccessible (n=3041)	Biologics Accessible but Not Received (n=382)	Biologics Accessible and Received (n=4651)	Biologic Recipients Whose Asthma Remained Suboptimally Controlled (n=3346)
Age, years, mean (SD)	54.1 (14.3)	57.2 (15.1)	56.3 (15.4)	54.0 (14.2)	54.5 (14.0)
Female, n (%)	3212 (63.3)	1924 (63.3)	260 (68.1)	2932 (63.0)	2119 (63.3)
BMI, kg/m^2, mean (SD)	28.5 (9.9)	29.6 (10.1)	29.5 (7.4)	28.4 (10.1)	28.5 (10.2)
<18	59 (1.3)	29 (1.0)	4 (1.1)	54 (1.3)	32 (1.1)
≥18 to <25	1442 (31.6)	805 (28.7)	109 (29.8)	1324 (31.8)	953 (31.8)
≥25 to <30	1546 (33.9)	888 (31.6)	100 (27.3)	1430 (34.4)	1018 (34.0)
≥30	1515 (33.2)	1085 (38.7)	153 (41.8)	1349 (32.5)	991 (33.1)
Smoking status, n (%)					
Current	155 (3.5)	228 (8.4)	27 (7.7)	127 (3.1)	82 (2.8)
Former	1169 (26.3)	870 (32.1)	104 (29.7)	1052 (25.9)	759 (26.3)
Never	3123 (70.2)	1613 (59.5)	219 (62.6)	2879 (70.9)	2040 (70.8)
Smoking duration, pack-years, mean (SD)	17.2 (17.7)	20.1 (29.1)	18.7 (17.3)	17.0 (17.8)	17.7 (18.5)
Asthma duration, years, mean (SD)	23.7 (16.1)	22.3 (17.3)	19.9 (14.4)	23.8 (16.2)	24.5 (16.5)
GINA step, n (%)					
4	807 (15.9)	2635 (86.6)	295 (77.2)	512 (11.0)	305 (9.1)
5	4266 (84.1)	406 (13.4)	87 (22.8)	4139 (89.0)	3041 (90.9)
Pre-bronchodilator FEV_1, L, mean (SD)	1.9 (0.8)	1.9 (0.8)	1.6 (0.7)	1.9 (0.8)	1.9 (0.8)
Pre-bronchodilator FVC, L, mean (SD)	2.8 (1.1)	2.7 (1.0)	2.5 (0.9)	2.9 (1.1)	2.8 (1.2)
Post-bronchodilator FEV_1, L, mean (SD)	2.0 (0.8)	2.0 (0.8)	1.7 (0.7)	2.0 (0.8)	2.0 (0.8)
FeNO, ppb					
Mean (SD)	48.9 (46.0)	37.7 (35.9)	35.2 (33.0)	49.3 (46.3)	50.8 (47.8)
≥25 ppb, n (%)	1327 (63.5)	377 (50.9)	40 (47.6)	1283 (63.9)	993 (64.6)
Blood eosinophil count, cells/μL					
Mean (SD)	620.3 (834.4)	386.2 (476.4)	526.1 (570.5)	631.7 (855.2)	604.4 (875.6)
≥300 cells/μL, n (%)	1855 (65.6)	764 (46.3)	151 (64.5)	1704 (65.9)	1173 (61.5)
Serum total IgE, IU/mL					
Mean (SD)	525.9 (1334.8)	369.9 (796.2)	514.7 (903.0)	527.5 (1357.0)	515.4 (921.9)
≥75 IU/mL, n (%)	2086 (78.5)	687 (64.6)	91 (67.9)	1986 (79.2)	1420 (79.5)
Comorbidities, n (%)					
Allergic rhinitis	2506 (52.0)	1315 (56.9)	192 (63.0)	2299 (51.3)	1672 (51.3)
Chronic rhinosinusitis	1939 (40.2)	1036 (44.8)	180 (59.0)	1741 (38.8)	1253 (38.4)
Nasal polyps	1547 (32.1)	325 (14.1)	50 (16.4)	1493 (33.3)	1096 (33.6)
Atopic disease	2107 (43.7)	780 (33.7)	109 (35.7)	1996 (44.5)	1536 (47.1)
GERD	956 (46.0)	1016 (54.2)	159 (68.8)	778 (42.7)	541 (42.8)
Pneumonia	219 (7.4)	104 (4.8)	12 (3.9)	205 (7.7)	174 (8.9)

Notes: The baseline period was the 12-month period before the index date, defined as the first visit recorded in ISAR with measurements meeting the group eligibility criteria. Percentages exclude patients with missing data.

Abbreviations: BMI, body mass index; FeNO, fractional exhaled nitric oxide; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; GERD, gastroesophageal reflux disease; GINA, Global Initiative for Asthma; IgE, immunoglobulin E; ISAR, International Severe Asthma Registry; SD, standard deviation.

68.1% across groups), had a mean age of approximately 55 years, and had a mean asthma duration of approximately 20–25 years. Pre-bronchodilator forced expiratory volume in 1 second values were similar across groups (mean: 1.9 L) except for the biologics accessible but not received group (mean: 1.6 L). Approximately half of the patients in the biologics inaccessible and biologics accessible but not received groups, and approximately two-thirds of patients in the other groups, had FeNO levels of at least 25 ppb. Furthermore, approximately two-thirds of patients across groups had a blood eosinophil count of at least 300 cells/μL, except for the biologics inaccessible group (46.3%). Chronic rhinosinusitis was present in approximately 40% of patients across groups, but was more common in the biologics accessible but not received group (59.0%), while nasal polyps were present in approximately one-third of patients in the biologics accessible and biologic recipient groups.

Asthma Burden at Baseline

In the biologics accessible group, 41.4% of patients experienced at least two exacerbations during the 12-month baseline period (Figure 2A), whereas 16.2% had at least one ER visit and 11.5% had at least one hospital admission (Table 2). The proportion of patients with uncontrolled asthma during this period was 47.9% (Figure 2B), and the proportion receiving LTOCS was 23.9% (Figure 2C). Use of non-biologic add-on controller medications is shown in Supplementary Table 5.

In the biologics inaccessible group, 18.7% of patients experienced at least two exacerbations during the baseline period (Figure 2A), whereas 8.8% had at least one ER visit and 10.5% had at least one hospital admission (Table 2); 54.6% had uncontrolled asthma during this period (Figure 2B) and 8.6% were receiving LTOCS (Figure 2C).

In the biologics accessible but not received group, 49.6% of patients experienced at least two exacerbations (Figure 2A), 14.4% had at least one ER visit, and 6.2% had at least one hospital admission (Table 2); 71.2% had uncontrolled asthma (Figure 2B) and 11.0% were receiving LTOCS (Figure 2C).

In the biologics accessible and received group (ie, biologic recipients), 40.7% of patients experienced at least two exacerbations (Figure 2A), 16.4% had at least one ER visit, and 12.0% had at least one hospital admission (Table 2); 46.9% had uncontrolled asthma (Figure 2B) and 25.0% were receiving LTOCS (Figure 2C).

Asthma Burden Following Biologic Therapy

Among biologic recipients overall, 19.1% experienced at least two exacerbations during the 12 months following biologic treatment (Figure 2A), ranging from 17.3% for anti-IgE recipients to 22.3% for anti–IL-5R recipients (Supplementary Table 6). The proportion of biologic recipients overall who had at least one ER visit during this period was 5.9%, whereas 2.7% had at least one hospital admission. Approximately one-third of biologic recipients experienced uncontrolled asthma following biologic treatment (32.4% for biologic recipients overall; Figure 2B), ranging from 28.6% (for anti-IgE and anti–IL-4/13) to 35.7% (for anti-IL-5; Supplementary Table 6). The proportion of patients who received LTOCS during the follow-up period was 16.7% among biologic recipients overall (Table 2, Figure 2C), ranging from 11.5% for anti-IgE recipients to 20.3% for anti–IL-5 recipients (Supplementary Table 7).

Among biologic recipients whose asthma remained suboptimally controlled despite therapy, 23.0% of patients experienced at least two exacerbations during the follow-up period (Figure 2A), whereas 6.9% had at least one ER visit and 2.9% had at least one hospital admission (Table 2). The proportion of patients in this group who received LTOCS during the follow-up period was 22.0% (Figure 2C).

Discussion

A substantial disease burden was observed across the groups of patients with severe asthma studied here, including among patients who lacked access to T2-targeted biologics (omalizumab, mepolizumab, reslizumab, benralizumab, or dupilumab) and among those who had access but who did not receive these treatments during the study period. Among patients who did receive these biologics, a sizable proportion still experienced a considerable burden in terms of exacerbations, HCRU, asthma control, and LTOCS use.

Among the patients who lacked access to T2-targeted biologic therapy, approximately 40% experienced at least one exacerbation and over 50% had uncontrolled asthma during the 12-month baseline period. These findings suggest that many of these patients may require different therapy options. Prescription eligibility criteria and reimbursement

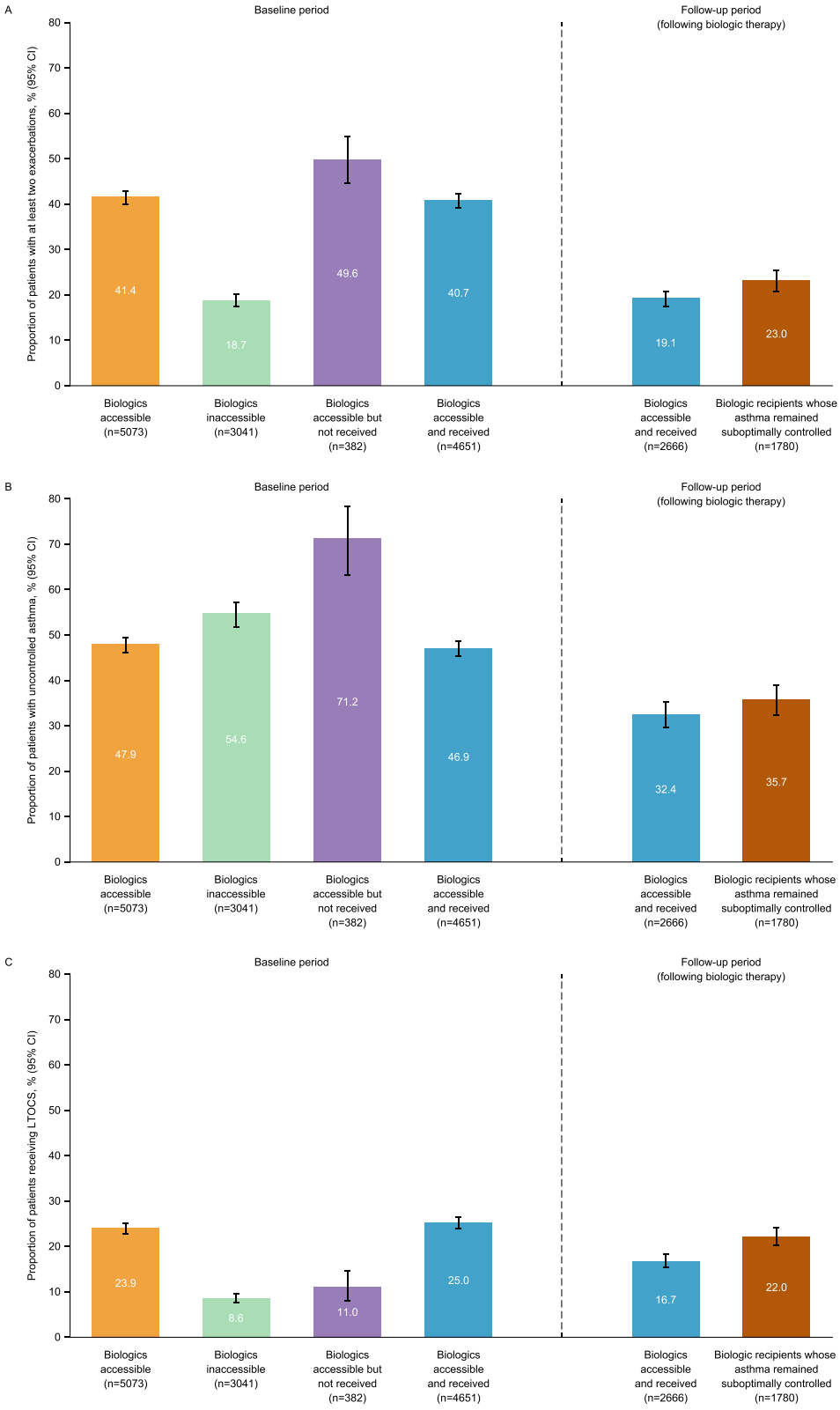

Figure 2 Proportions of patients with severe asthma who experienced at least two exacerbations (**A**), who had uncontrolled asthma (**B**), or who were receiving LTOCS (**C**) during the baseline period and follow-up period (following biologic therapy), by biologic accessibility and use.

Notes: Biologic accessibility/use was for therapies that were licensed during the study period (ie, omalizumab, mepolizumab, reslizumab, benralizumab, and dupilumab). The results reported here exclude missing data. The baseline period was the 12 months before the index date, defined as the first visit recorded in ISAR with measurements meeting the group eligibility criteria. The follow-up period was the 12 months after the index date. In panel B, asthma control as an outcome was assessed using GINA 2019 criteria.[41] This differs from the group definition for biologic recipients whose asthma remained suboptimally controlled (see Figure 1).

Abbreviations: CI, confidence interval; GINA, Global Initiative for Asthma; ISAR, International Severe Asthma Registry; LTOCS, long-term oral corticosteroid.

Table 2 Asthma-Related Healthcare Resource Utilization During the Baseline Period and Follow-Up Period (Following Biologic Therapy)

	Baseline Period				Follow-up Period	
	Biologics Accessible (n=5073)	**Biologics Inaccessible (n=3041)**	**Biologics Accessible but Not Received (n=382)**	**Biologics Accessible and Received (n=4651)**	**Biologics Accessible and Received (n=2666)**	**Biologic Recipients Whose Asthma Remained Suboptimally Controlled (n=1780)**
Asthma exacerbations						
Mean (SD)	1.97 (3.16)	0.88 (1.75)	1.69 (1.71)	2.01 (3.27)	0.89 (1.89)	0.99 (1.88)
n (%) [95% CI]						
≥1	2799 (59.0) [57.6–60.4]	1237 (41.0) [39.3–42.8]	265 (69.9) [65.0–74.5]	2520 (58.3 [56.8–59.7]	701 (38.7) [36.5–41.0]	525 (42.2) [39.4–45.0]
≥2	1963 (41.4) [40.0–42.8]	565 (18.7) [17.4–20.2]	188 (49.6) [44.5–54.8]	1761 (40.7) [39.2–42.2]	345 (19.1) [17.3–20.9]	286 (23.0) [20.7, 25.4]
≥4	858 (18.1) [17.0–19.2]	166 (5.5) [4.7–6.4]	47 (12.4) [9.3–16.1]	811 (18.7) [17.6–19.9]	112 (6.2) [5.1–7.4]	92 (7.4) [6.0–9.0]
ER visits						
Mean (SD)	0.53 (2.18)	0.23 (1.19)	0.52 (1.77)	0.54 (2.22)	0.13 (0.82)	0.16 (0.95)
n (%) [95% CI]						
≥1	810 (16.2) [15.2–17.2]	265 (8.8) [7.8–9.9]	55 (14.4) [11.0–18.3]	753 (16.4) [15.4–17.5]	112 (5.9) [4.9–7.1]	90 (6.9) [5.6–8.5]
≥2	466 (9.3) [8.5–10.1]	136 (4.5) [3.8–5.3]	40 (10.5) [7.6–14.0]	425 (9.3) [8.4–10.1]	56 (3.0) [2.2–3.8]	43 (3.3) [2.4–4.4]
≥4	205 (4.1) [3.6–4.7]	45 (1.5) [1.1–2.0]	19 (5.0) [3.0–7.7]	184 (4.0) [3.5–4.6]	16 (0.8) [0.5–1.4]	13 (1.0) [0.5–1.7]
Invasive ventilations						
Mean (SD)	0.03 (0.30)	0.02 (0.59)	0.03 (0.20)	0.03 (0.30)	0.00 (0.06)	0.00 (0.00)
n (%) [95% CI]						
≥1	82 (1.9) [1.5–2.3]	28 (1.0) [0.7–1.4]	6 (1.7) [0.6–3.6]	74 (1.9) [1.5–2.3]	4 (0.2) [0.1–0.6]	0 (0.0) [0.0–0.3]
Hospital admissions						
Mean (SD)	0.25 (1.26)	0.16 (0.56)	0.11 (0.49)	0.26 (1.31)	0.05 (0.61)	0.06 (0.72)
n (%) [95% CI]						
≥1	545 (11.5) [10.6–12.5]	305 (10.5) [9.4–11.7]	22 (6.2) [3.9–9.2]	522 (12.0) [11.1–13.0]	50 (2.7) [2.0–3.6]	36 (2.9) [2.0–3.9]
≥2	223 (4.7) [4.1–5.4]	98 (3.4) [2.8–4.1]	12 (3.4) [1.8–5.8]	211 (4.9) [4.2–5.5]	13 (0.7) [0.4–1.2]	10 (0.8) [0.4–1.5]
≥4	74 (1.6) [1.2–2.0]	13 (0.4) [0.2–0.8]	0 (0.0) [0.0–1.0]	74 (1.7) [1.3–2.1]	1 (0.1) [0.0–0.3]	1 (0.1) [0.0–0.4]

Notes: Biologic accessibility/use was for therapies that were licensed during the study period (ie, omalizumab, mepolizumab, reslizumab, benralizumab, and dupilumab). The baseline period was the 12 months before the index date, defined as the first visit recorded in ISAR with measurements meeting the group eligibility criteria. The follow-up period was the 12-month period after the index date. Percentages exclude patients with missing values.
Abbreviations: CI, confidence interval; ER, emergency room; ISAR, International Severe Asthma Registry; SD, standard deviation.

https://doi.org/10.2147/JAA.S468068 DovePress

availability for biologics vary substantially between countries,[23] which may reflect a lack of consensus regarding which patients benefit most from which therapy. It was notable that approximately half of the patients who could not access T2 biologics had elevated FeNO levels (≥25 ppb) and/or elevated blood eosinophil counts (≥300 cells/μL), and approximately two-thirds had elevated serum total IgE levels (≥75 IU/mL) at baseline. These findings imply that many of the patients in this group did not have true T2-low phenotypes; rather, the fact that these patients did not qualify for access to T2 biologics according to the country-specific BACS criteria may indicate that the prescription eligibility criteria used in some countries are suboptimal. The dynamic nature of asthma phenotypes, including levels of inflammatory biomarkers, should also be considered;[42] if applied too rigidly, phenotyping may not always help with appropriate biologic selection and may unnecessarily restrict patient eligibility.

In this study, 7.5% of patients who qualified for access to T2-targeted biologic therapy did not receive it. Various factors may have contributed to this, including limited availability of biologics and severe asthma services.[23] Indeed, a large proportion of the global asthma population that may be eligible for biologics is not receiving them.[43,44] In this study, patients who had access to T2-targeted biologic therapy but did not receive it had a very high burden of disease, with half experiencing at least two exacerbations and more than two-thirds having uncontrolled asthma during the baseline period. These findings highlight the impact of not prescribing biologic therapies to eligible patients.

Approximately half of the overall patient cohort in this study were prescribed a biologic therapy, a higher proportion than observed in a similar ISAR cohort using data from 2014–2017 (approximately one-quarter),[38] indicative of the growing use of biologics worldwide. However, a sizable disease burden was observed here among biologic recipients overall despite use of these treatments, with one-fifth experiencing at least two exacerbations and one-third having uncontrolled asthma during the 12-month follow-up period. Furthermore, over two-thirds of biologic recipients had asthma that remained suboptimally controlled despite treatment with a biologic. A direct comparison of patients' disease burden pre- and post-treatment was not performed, so these results should not be interpreted as an analysis of the effectiveness of the biologic therapies received. The impact of T2-targeted biologic therapy in real-world severe asthma cohorts has been assessed previously, finding that these therapies generally improve the outcomes assessed, such as exacerbation rates, asthma control, lung function, OCS exposure, and HCRU.[12,45–47]

A contributing factor to the considerable remaining disease burden among biologic recipients may have been the presence of symptoms resulting from comorbidities such as chronic rhinosinusitis and nasal polyps. However, it was largely expected that the disease burden would remain high among patients who received biologic treatment with omalizumab, mepolizumab, reslizumab, benralizumab, or dupilumab, because these therapies have been shown to produce only an approximate 50% reduction in exacerbation rates in clinical trial populations,[13–15] while approximately 30–50% of patients in real-world studies achieve remission when treated with these biologics (although definitions of remission vary).[48–50] The mechanisms of the biologics studied here (anti-IgE, anti–IL-5/IL-5R, and anti–IL-4/13) are most effective in patients with high baseline levels of T2 inflammatory biomarkers, such as blood eosinophil counts (≥260–300 cells/μL) and FeNO levels (≥25 ppb), while demonstrating reduced or negligible efficacy in patients with low T2 biomarker levels.[51–55] Biologics with broader actions on asthma disease mechanisms, particularly those whose mechanisms reach beyond T2 inflammation, may be licensed for the treatment of severe asthma without biomarker or phenotypic restrictions, widening eligibility compared with the T2-targeted biologics. These include the recently introduced tezepelumab,[22] a human monoclonal antibody that blocks the activity of thymic stromal lymphopoietin, an upstream mediator of inflammation in asthma that also has T2-independent effects.[56] However, owing to its recent approval, insufficient data were available for tezepelumab to be included in the present study. Further targets under investigation for biologic therapy in severe asthma include the IL-33/ST2 pathway, IL-6, OX40 ligand, and TNF-like ligand 1A.[57–62] Future real-world studies to assess clinical characteristics and HCRU among patients who receive newly approved biologics such as tezepelumab are needed to better understand the remaining unmet medical need in patients with severe asthma.

The variation in biologic accessibility criteria between the participating countries in this study meant that biologic recipients accessed these therapies at different stages of disease severity. Furthermore, health system complexities and potential delays in referral to specialists in some countries[24,63,64] may have caused patients to experience delays in receiving appropriate care, including biologic therapies. Because longer asthma duration may be associated with

a weaker response to biologics,[65] the benefits of early biologic initiation in reducing the observed disease burden in patients with severe asthma should be investigated in future studies.

A strength of the present study is the use of ISAR, which provides a large global data set of the characteristics of patients with severe asthma and their treatment. The database consists of high-quality, patient-level, real-world, standardized data collected from multiple countries. However, the differences between countries' healthcare systems (including biologic accessibility criteria) described above, as well as the differences in patient characteristics between the registries included in ISAR and in the amount of missing data in each registry, influenced assignment of patients to the different groups used here and constrain the generalizability of this study's findings. The considerable variation in the observed disease burden of patients with severe asthma from different registries is clear in a recent systematic review.[66] Missing data are an inherent challenge in real-world research: 15% of patients in the overall ISAR cohort here had insufficient data to determine biologic accessibility, and over 40% of biologic recipients could not be included in the follow-up period analysis. Furthermore, despite best efforts at standardization, there was inevitable variability in data recording quality and practices across the many countries and sites involved in this study. For instance, although most countries recorded exacerbations directly, in the US, exacerbations were captured by proxy via OCS use. The use of prescriptions as a proxy for receiving biologic therapy was another limitation, because in some countries patients may be prescribed biologics but not actually receive them if not covered by health insurance. A further limitation is that the study was not designed to perform statistical comparisons between groups – future studies that are designed to compare disease burden between relevant subgroups should be considered. Finally, the study did not evaluate changes in medication use, such as switching biologics, or the reasons for any lack of effectiveness of the biologic therapies received – this has been assessed previously in a similar ISAR cohort.[67]

Conclusions

Descriptive disease burden data provide important information to healthcare researchers and policymakers; these data may prompt strategies to improve healthcare delivery and treatment, and help in planning future need, setting resource priority, and informing future research. Data regarding the disease burden experienced by various subgroups of patients with severe asthma – for example, those with and without access to biologic therapy – are limited in the literature. However, this evidence is critical for understanding these patients' unmet need and for informing development strategies of new treatments. The global real-world data reported here suggest a persistently high disease burden among patients with severe asthma who lack access to T2-targeted biologics and among those who have access but do not receive them. The results also highlight the remaining disease burden among patients currently receiving therapy with these biologics. Overall, the substantial unmet medical need in this population indicates the need for regulators to increase and standardize access to biologics and for researchers to develop more effective therapy options to improve the management of patients with severe asthma.

Data Sharing Statement

The dataset supporting the conclusions of this article was derived from the International Severe Asthma Registry (ISAR). This study was approved by the Anonymised Data Ethics Protocols and Transparency (ADEPT) committee – the independent scientific advisory committee for ISAR. The authors do not have permission to give public access to the study dataset; researchers may request access to ISAR data for their own purposes. ISAR research requests and proposals can be made via the ISAR website (https://isaregistries.org/research-proposal-requests/) or via the enquiries Email to info@isaregistries.org. In line with ISAR governance restrictions, sharing individual deidentified participant data is subject to the consent of the ISAR steering committee in accordance with patient consent, patient confidentiality and ethical considerations. The study documents (protocol, statistical analysis plan, clinical study report) will be made available in accordance with the criteria of the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (EUPAS38128). Proposals should be directed to info@isaregistries.org; to gain access, if approved by the regulatory boards, data requestors will need to sign a data access agreement.

Ethical Approval and Informed Consent

The study was designed, implemented, and reported in compliance with the European Network Centres for Pharmacoepidemiology and Pharmacovigilance Code of Conduct (registration number: EUPAS106967) and with all applicable local and international laws and regulations. Registration of the ISAR database with the European Union Electronic Register of Post-Authorization studies was also undertaken (ENCEPP/DSPP/23720). Ethical governance for ISAR was provided by ADEPT (approval reference number: ADEPT-1021). All data collection sites in ISAR have obtained regulatory agreement in compliance with specific data transfer laws, country-specific legislation, and relevant ethical boards and organizations. The study was approved by the ISAR International Steering Committee and was performed in accordance with the 1964 Declaration of Helsinki and its later amendments. All participating patients provided informed consent, and their data were anonymized.

Acknowledgments

The authors thank all the ISAR collaborators (Appendix 1) and study participants, and Ekaterina Maslova of AstraZeneca for her contributions to the study design. Medical writing support was provided by Priyanka Narang, PhD, and Richard Claes, PhD, of PharmaGenesis London, London, UK, with funding from AstraZeneca.

Collaborators: EVEREST Study Working Group

Mona Al-Ahmad, Riyad Al-Lehebi, Peter Barker, Leif Bjermer, John Busby, Giorgio Walter Canonica, Borja G Cosio, Richard Costello, João A Fonseca, Peter G Gibson, Liam G Heaney, Enrico Heffler, Mark Hew, Takashi Iwanaga, David J Jackson, Piotr Kuna, Désirée Larenas Linnemann, Sverre Lehmann, Jorge Maspero, Andrew Menzies-Gow, Andriana I Papaioannou, Diahn-Warng Perng, Matthew Peters, Todor A Popov, Celeste Porsbjerg, Mohsen Sadatsafavi, Sundeep Salvi, Camille Taillé, Carlos A Torres-Duque, Eileen Wang and Michael E Wechsler.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This study was funded by AstraZeneca. ISAR is jointly funded by Optimum Patient Care Global and AstraZeneca.

Disclosure

Tham T. Le, Clement Erhard, Bill Cook, Anna Quinton, Neil Martin, and Trung N. Tran are employees of AstraZeneca and may own stock or stock options in AstraZeneca. David B Price has participated in advisory boards with Amgen, AstraZeneca, Boehringer Ingelheim, Chiesi, Circassia, Mundipharma, Novartis, Regeneron Pharmaceuticals, Sanofi Genzyme, Teva Pharmaceuticals, Thermo Fisher, and Viatris; has consultancy agreements with Amgen, AstraZeneca, Boehringer Ingelheim, Chiesi, Cipla, GSK, Medscape, Mundipharma, Novartis, Pfizer, Teva Pharmaceuticals, Theravance, and Viatris; has received grants and unrestricted funding for investigator-initiated studies (conducted through Observational and Pragmatic Research Institute Pte Ltd) from AstraZeneca, Boehringer Ingelheim, Chiesi, Circassia, Mundipharma, Novartis, Pfizer, Regeneron Pharmaceuticals, Sanofi Genzyme, Teva Pharmaceuticals, Theravance, the UK National Health Service, and Viatris; has received payment for lectures/speaking engagements from AstraZeneca, Boehringer Ingelheim, Chiesi, Cipla, GSK, Mundipharma, Novartis, Pfizer, Regeneron Pharmaceuticals, Sanofi Genzyme, Teva Pharmaceuticals, and Viatris; has received payment for travel/accommodation/meeting expenses from AstraZeneca, Boehringer Ingelheim, Circassia, Mundipharma, Novartis, Teva Pharmaceuticals, and Thermo Fisher; has received funding for patient enrollment or completion of research from Novartis; has stock or stock options with AKL Research and Development Ltd; owns 74% of the social enterprise Optimum Patient Care Ltd (Australia and UK) and 74% of Observational and Pragmatic Research Institute Pte Ltd

(Singapore); owns 5% shareholding in Timestamp; is a peer reviewer for Health Technology Assessment and the grant committees of the UK Efficacy and Mechanism Evaluation Programme; and was an expert witness for GSK. Rohit Katial is a former employee of AstraZeneca and has been an advisory board participant and speaker for GSK and Sanofi/Regeneron. Luis Perez-de-Llano has received grants from AstraZeneca, Chiesi, and Teva Pharmaceuticals; personal fees from AstraZeneca, Boehringer Ingelheim, Chiesi, Esteve, FAES, GEBRO, GSK, Mundipharma, Novartis, Sanofi, and Teva Pharmaceuticals; and nonfinancial support from Boehringer Ingelheim, Esteve, GSK, Menarini, Mundipharma, Novartis, and Teva Pharmaceuticals. Alan Altraja has received lecture fees from AstraZeneca, Berlin-Chemie Menarini, Boehringer Ingelheim, CSL Behring, GSK, MSD, Norameda, Novartis, Orion, Sanofi Regeneron, and Zentiva; sponsorships from AstraZeneca, Berlin-Chemie Menarini, Boehringer Ingelheim, CSL Behring, GSK, MSD, Norameda, Novartis, and Sanofi Regeneron; and has participated in advisory boards for AstraZeneca, Boehringer Ingelheim, CSL Behring, GSK, Novartis, Sanofi Regeneron, and Teva Pharmaceuticals. Celine Bergeron has participated in advisory boards for GSK, Sanofi-Regeneron, AstraZeneca, Amgen, Takeda, and Valeo Pharma; has received honoraria for presentations for AstraZeneca, Amgen, Grifols, GSK, Sanofi-Regeneron, and Valeo Pharma; and her institution has received grants from AstraZeneca, Biohaven, GSK, OPRI/ISAR, Novartis, Sanofi-Regeneron and Teva. Arnaud Bourdin has received industry-sponsored grants from AstraZeneca, Boehringer Ingelheim, Cephalon/Teva, GSK, Novartis, and Sanofi-Regeneron; and been a consultant for Actelion, AstraZeneca, Boehringer Ingelheim, Chiesi, GSK, MedinCell, Merck, Novartis, Regeneron-Sanofi, and Roche. Mariko Siyue Koh has received grants from AstraZeneca; and honoraria for lectures and advisory board meetings paid to her hospital (Singapore General Hospital) from GSK, AstraZeneca, Boehringer Ingelheim, Novartis, Roche, and Sanofi. Lauri Lehtimäki has received personal fees from ALK, AstraZeneca, Berlin-Chemie, Boehringer Ingelheim, Chiesi, GSK, Menarini, Novartis, Orion Pharma, and Sanofi. Nikolaos G Papadopoulos has been a speaker and/or advisory board member for Abbott, AbbVie, ALK, Asit Biotech, AstraZeneca, Biomay, Boehringer Ingelheim, GSK, HAL, Faes Farma, Medscape, Menarini, MSD, Mylan, Novartis, Nutricia, OM Pharma, Regeneron, Sanofi, Takeda, and Viatris. Paul Pfeffer has attended advisory boards for AstraZeneca, GSK, and Sanofi; has given lectures at meetings supported by AstraZeneca and GSK; has taken part in clinical trials sponsored by AstraZeneca, GSK, Novartis, and Sanofi, for which his institution received remuneration; has received speaker fee from Chiesi for an educational webinar and has a current research grant funded by GSK. Chin Kook Rhee received consulting/lecture fees from AstraZeneca, Bayer, Boehringer Ingelheim, GSK, MSD, Mundipharma, Novartis, Sanofi, Takeda, and Teva. Victoria Carter is an employee of Optimum Patient Care, a co-funder of ISAR. The authors report no other conflicts of interest in this work.

References

1. World Health Organization. Fact sheets: asthma. 2023. Available from: https://www.who.int/news-room/fact-sheets/detail/asthma. Accessed February 22, 2024.
2. Backman H, Jansson SA, Stridsman C, et al. Severe asthma-A population study perspective. *Clin Exp Allergy*. 2019;49(6):819–828. doi:10.1111/cea.13378
3. Ronnebjerg L, Axelsson M, Kankaanranta H, et al. Severe asthma in a general population study: prevalence and clinical characteristics. *J Asthma Allergy*. 2021;14:1105–1115. doi:10.2147/JAA.S327659
4. Larsson K, Stallberg B, Lisspers K, et al. Prevalence and management of severe asthma in primary care: an observational cohort study in Sweden (PACEHR). *Respir Res*. 2018;19(1):12. doi:10.1186/s12931-018-0719-x
5. Global Initiative for Asthma. Global strategy for asthma management and prevention. 2023. Available from: https://ginasthma.org/wp-content/uploads/2023/07/GINA-2023-Full-report-23_07_06-WMS.pdf. Accessed February 22, 2024.
6. Chung KF, Wenzel SE, Brozek JL, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. *Eur Respir J*. 2014;43(2):343–373. doi:10.1183/09031936.00202013
7. Zeiger RS, Schatz M, Dalal AA, et al. Utilization and costs of severe uncontrolled asthma in a managed-care setting. *J Allergy Clin Immunol Pract*. 2016;4(1):120–129. doi:10.1016/j.jaip.2015.08.003
8. Kerkhof M, Tran TN, Soriano JB, et al. Healthcare resource use and costs of severe, uncontrolled eosinophilic asthma in the UK general population. *Thorax*. 2018;73(2):116–124. doi:10.1136/thoraxjnl-2017-210531
9. Hossny E, Caraballo L, Casale T, El-Gamal Y, Rosenwasser L. Severe asthma and quality of life. *World Allergy Organ J*. 2017;10(1):28. doi:10.1186/s40413-017-0159-y
10. Sardon-Prado O, Diaz-Garcia C, Corcuera-Elosegui P, Korta-Murua J, Valverde-Molina J, Sanchez-Solis M. Severe asthma and biological therapies: now and the future. *J Clin Med*. 2023;12(18):5846. doi:10.3390/jcm12185846
11. Mohan A, Qiu AY, Lugogo N. Long-term safety, durability of response, cessation and switching of biologics. *Curr Opin Pulm Med*. 2024;30(3):303–312. doi:10.1097/MCP.0000000000001067

12. Nagase H, Suzukawa M, Oishi K, Matsunaga K. Biologics for severe asthma: the real-world evidence, effectiveness of switching, and prediction factors for the efficacy. *Allergol Int*. 2023;72(1):11–23. doi:10.1016/j.alit.2022.11.008
13. Farne HA, Wilson A, Powell C, Bax L, Milan SJ. Anti-IL5 therapies for asthma. *Cochrane Database Syst Rev*. 2017;9:CD010834. doi:10.1002/14651858.CD010834.pub3
14. Normansell R, Walker S, Milan SJ, Walters EH, Nair P. Omalizumab for asthma in adults and children. *Cochrane Database Syst Rev*. 2014;(1):CD003559. doi:10.1002/14651858.CD003559.pub4
15. Zayed Y, Kheiri B, Banifadel M, et al. Dupilumab safety and efficacy in uncontrolled asthma: a systematic review and meta-analysis of randomized clinical trials. *J Asthma*. 2019;56(10):1110–1119. doi:10.1080/02770903.2018.1520865
16. Kyriakopoulos C, Gogali A, Markozannes G, Kostikas K. Biologic agents licensed for severe asthma: a systematic review and meta-analysis of randomised controlled trials. *Eur Respir Rev*. 2024;33(172):230238. doi:10.1183/16000617.0238-2023
17. US Food & Drug Administration. NUCALA (mepolizumab) prescribing information. 2015. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/125526Orig1s000Lbl.pdf. Accessed February 22, 2024.
18. US Food & Drug Administration. CINQAIR (reslizumab) prescribing information; 2016. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/761033lbl.pdf. Accessed February 22, 2024.
19. US Food & Drug Administration. Dupixent (dupilumab) prescribing information; 2017. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/761055lbl.pdf. Accessed February 22, 2024.
20. US Food & Drug Administration. FASENRA (benralizumab) prescribing information; 2017. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/761070s000lbl.pdf. Accessed February 22, 2024.
21. US Food & Drug Administration. ZOLAIR (omalizumab) prescribing information; 2021. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2003/omalgen062003LB.pdf. Accessed February 22, 2024.
22. US Food & Drug Administration. TEZSPIRE (tezepelumab) prescribing information; 2021. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/761224s001lbl.pdf. Accessed February 22, 2024.
23. Porsbjerg CM, Menzies-Gow AN, Tran TN, et al. Global variability in administrative approval prescription criteria for biologic therapy in severe asthma. *J Allergy Clin Immunol Pract*. 2022;10(5):1202–1216.e1223. doi:10.1016/j.jaip.2021.12.027
24. Bordbar N, Shojaei P, Ravangard R, Bastani P, Joulaei H, Kavosi Z. Evaluation of the world countries health referral system performance based on world health organization indicators using hybrid multi-criteria decision-making model. *Value Health Reg Issues*. 2022;28:19–28. doi:10.1016/j.vhri.2021.06.006
25. Marques Mello L, Viana KP, Moraes Dos Santos F, et al. Severe asthma and eligibility for biologics in a Brazilian cohort. *J Asthma*. 2021;58(7):958–966. doi:10.1080/02770903.2020.1748049
26. Akenroye AT, Heyward J, Keet C, Alexander GC. Lower use of biologics for the treatment of asthma in publicly insured individuals. *J Allergy Clin Immunol Pract*. 2021;9(11):3969–3976. doi:10.1016/j.jaip.2021.01.039
27. Inselman JW, Jeffery MM, Maddux JT, Shah ND, Rank MA. Trends and disparities in asthma biologic use in the United States. *J Allergy Clin Immunol Pract*. 2020;8(2):549–554e541. doi:10.1016/j.jaip.2019.08.024
28. Chen W, Sadatsafavi M, Tran TN, et al. Characterization of patients in the international severe asthma registry with high steroid exposure who did or did not initiate biologic therapy. *J Asthma Allergy*. 2022;15:1491–1510. doi:10.2147/JAA.S377174
29. Carr TF, Zeki AA, Kraft M. Eosinophilic and noneosinophilic asthma. *Am J Respir Crit Care Med*. 2018;197(1):22–37. doi:10.1164/rccm.201611-2232PP
30. Hinks TSC, Levine SJ, Brusselle GG. Treatment options in type-2 low asthma. *Eur Respir J*. 2021;57(1):2000528. doi:10.1183/13993003.00528-2020
31. Akenroye A, McCormack M, Keet C. Severe asthma in the US population and eligibility for mAb therapy. *J Allergy Clin Immunol*. 2020;145(4):1295–1297e1296. doi:10.1016/j.jaci.2019.12.009
32. Heffler E, Blasi F, Latorre M, et al. The severe asthma network in Italy: findings and perspectives. *J Allergy Clin Immunol Pract*. 2019;7(5):1462–1468. doi:10.1016/j.jaip.2018.10.016
33. Jackson DJ, Busby J, Pfeffer PE, et al. Characterisation of patients with severe asthma in the UK severe asthma registry in the biologic era. *Thorax*. 2021;76(3):220–227. doi:10.1136/thoraxjnl-2020-215168
34. Kim MH, Kim SH, Park SY, et al. Characteristics of adult severe refractory asthma in Korea analyzed from the severe asthma registry. *Allergy Asthma Immunol Res*. 2019;11(1):43–54. doi:10.4168/aair.2019.11.1.43
35. FitzGerald JM, Tran TN, Alacqua M, et al. International severe asthma registry (ISAR): protocol for a global registry. *BMC Med Res Methodol*. 2020;20(1):212. doi:10.1186/s12874-020-01065-0
36. ISAR Study Group. International severe asthma registry: mission statement. *Chest*. 2020;157(4):805–814. doi:10.1016/j.chest.2019.10.051
37. International Severe Asthma Registry. Available from: https://www.isar.opcglobal.org/. Accessed September 21, 2023.
38. Wang E, Wechsler ME, Tran TN, et al. Characterization of severe asthma worldwide: data from the international severe asthma registry. *Chest*. 2020;157(4):790–804. doi:10.1016/j.chest.2019.10.053
39. Respiratory Effectiveness Group. ADEPT (anonymised data ethics and protocol transparency) committee. Available from: https://www.regresearchnetwork.org/adept-committee/. Accessed February 22, 2024.
40. Global Initiative for Asthma. Global strategy for asthma management and prevention; 2018. Available from: https://ginasthma.org/wp-content/uploads/2019/01/2018-GINA.pdf. Accessed February 22, 2024.
41. Global Initiative for Asthma. Global strategy for asthma management and prevention; 2019. Available from: https://ginasthma.org/wp-content/uploads/2019/06/GINA-2019-main-report-June-2019-wms.pdf. Accessed February 22, 2024.
42. Ricciardolo FLM, Guida G, Bertolini F, Di Stefano A, Carriero V. Phenotype overlap in the natural history of asthma. *Eur Respir Rev*. 2023;32(168):220201. doi:10.1183/16000617.0201-2022
43. Menzies-Gow A, Tran TN, Hosseini N, et al. Global access for biologics in the treatment of severe asthma: a challenge to personalized medicine. *Am J Respir Crit Care Med*. 2020;201:A5954.
44. Tiew PY, Tay TR, Chen W, et al. Predictors of persistent poor control and validation of ASSESS score: longitudinal 5-year follow-up of severe asthma cohort. *J Allergy Clin Immunol Glob*. 2024;3(1):100188. doi:10.1016/j.jacig.2023.100188

45. Abbas F, Georas S, Cai X, Khurana S. Asthma biologics: real-world effectiveness, impact of switching biologics, and predictors of response. *Ann Allergy Asthma Immunol*. 2021;127(6):655–660e651. doi:10.1016/j.anai.2021.08.416
46. Chen W, Tran TN, Sadatsafavi M, et al. Impact of initiating biologics in patients with severe asthma on long-term oral corticosteroids or frequent rescue steroids (GLITTER): data from the international severe asthma registry. *J Allergy Clin Immunol Pract*. 2023;11(9):2732–2747. doi:10.1016/j.jaip.2023.05.044
47. Park SY, Lee SK, Song WJ, et al. Real-world effectiveness of biologics in patients with severe asthma: analysis of the KoSAR. *Allergy Asthma Immunol Res*. 2024;16(3):253–266. doi:10.4168/aair.2024.16.3.253
48. Maglio A, Vitale C, Pelaia C, et al. Severe asthma remissions induced by biologics targeting IL5/IL5R: results from a multicenter real-life study. *Int J Mol Sci*. 2023;24(3):2455. doi:10.3390/ijms24032455
49. Menzies-Gow A, Hoyte FL, Price DB, et al. Clinical remission in severe asthma: a pooled post hoc analysis of the patient journey with benralizumab. *Adv Ther*. 2022;39(5):2065–2084. doi:10.1007/s12325-022-02098-1
50. Pavord ID, Busse W, Israel E, et al. Dupilumab treatment leads to clinical asthma remission in patients with uncontrolled moderate-to-severe asthma with type 2 inflammation. *J Allergy Clin Immunol*. 2021;147(2 Suppl):AB4. doi:10.1016/j.jaci.2020.12.061
51. Albers FC, Licskai C, Chanez P, et al. Baseline blood eosinophil count as a predictor of treatment response to the licensed dose of mepolizumab in severe eosinophilic asthma. *Respir Med*. 2019;159:105806. doi:10.1016/j.rmed.2019.105806
52. FitzGerald JM, Bleecker ER, Menzies-Gow A, et al. Predictors of enhanced response with benralizumab for patients with severe asthma: pooled analysis of the SIROCCO and CALIMA studies. *Lancet Respir Med*. 2018;6(1):51–64. doi:10.1016/S2213-2600(17)30344-2
53. Hanania NA, Wenzel S, Rosen K, et al. Exploring the effects of omalizumab in allergic asthma: an analysis of biomarkers in the EXTRA study. *Am J Respir Crit Care Med*. 2013;187(8):804–811. doi:10.1164/rccm.201208-1414OC
54. Shrimanker R, Keene O, Hynes G, Wenzel S, Yancey S, Pavord ID. Prognostic and predictive value of blood eosinophil count, fractional exhaled nitric oxide, and their combination in severe asthma: a post hoc analysis. *Am J Respir Crit Care Med*. 2019;200(10):1308–1312. doi:10.1164/rccm.201903-0599LE
55. Perez de Llano L, Marina Malanda N, Urrutia I, et al. Factors associated with suboptimal response to monoclonal antibodies in severe asthma. *Allergy*. 2023;78(8):2305–2310. doi:10.1111/all.15693
56. Gauvreau GM, Sehmi R, Ambrose CS, Griffiths JM. Thymic stromal lymphopoietin: its role and potential as a therapeutic target in asthma. *Expert Opin Ther Targets*. 2020;24(8):777–792. doi:10.1080/14728222.2020.1783242
57. England E, Rees DG, Scott IC, et al. Tozorakimab (MEDI3506): an anti-IL-33 antibody that inhibits IL-33 signalling via ST2 and RAGE/EGFR to reduce inflammation and epithelial dysfunction. *Sci Rep*. 2023;13(1):9825. doi:10.1038/s41598-023-36642-y
58. Kelsen SG, Agache IO, Soong W, et al. Astegolimab (anti-ST2) efficacy and safety in adults with severe asthma: a randomized clinical trial. *J Allergy Clin Immunol*. 2021;148(3):790–798. doi:10.1016/j.jaci.2021.03.044
59. Wechsler ME, Ruddy MK, Pavord ID, et al. Efficacy and safety of Itepekimab in patients with moderate-to-severe asthma. *N Engl J Med*. 2021;385(18):1656–1668. doi:10.1056/NEJMoa2024257
60. ClinicalTrials.gov. A randomized, placebo controlled, double blind phase IIa study to evaluate the safety, tolerability, pharmacokinetics, and clinical activity of multiple intravenous doses of FB704A in adults with severe asthma. Available from: https://clinicaltrials.gov/study/NCT05018299. Accessed August 9, 2024.
61. ClinicalTrials.gov. A randomized, double-blind, placebo-controlled, parallel-group, dose ranging study to assess the efficacy, safety, and tolerability of subcutaneous amlitelimab in adult participants with moderate-to-severe asthma. Available from: https://clinicaltrials.gov/study/NCT05421598. Accessed August 9, 2024.
62. ClinicalTrials.gov. A 16-week, randomized, double-blind, placebo-controlled, parallel-group, proof-of-concept study to evaluate the efficacy and safety of TEV-48574 in adults with T2-low/non-T2 severe uncontrolled asthma. Available from: https://clinicaltrials.gov/study/NCT04545385. Accessed August 9, 2024.
63. Bloom CI, Walker S, Quint JK. Inadequate specialist care referrals for high-risk asthma patients in the UK: an adult population-based cohort 2006–2017. *J Asthma*. 2021;58(1):19–25. doi:10.1080/02770903.2019.1672723
64. Ryan D, Heatley H, Heaney LG, et al. Potential severe asthma hidden in UK primary care. *J Allergy Clin Immunol Pract*. 2021;9(4):1612–1623e1619. doi:10.1016/j.jaip.2020.11.053
65. Kroes JA, Zielhuis SW, van Roon EN, Ten Brinke A. Prediction of response to biological treatment with monoclonal antibodies in severe asthma. *Biochem Pharmacol*. 2020;179:113978. doi:10.1016/j.bcp.2020.113978
66. Czira A, Turner M, Martin A, et al. A systematic literature review of burden of illness in adults with uncontrolled moderate/severe asthma. *Respir Med*. 2022;191:106670. doi:10.1016/j.rmed.2021.106670
67. Menzies-Gow AN, McBrien C, Unni B, et al. Real world biologic use and switch patterns in severe asthma: data from the international severe asthma registry and the US CHRONICLE study. *J Asthma Allergy*. 2022;15:63–78. doi:10.2147/JAA.S328653