

# Characterization of Patients in the International Severe Asthma Registry with High Steroid Exposure Who Did or Did Not Initiate Biologic Therapy

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**Background:** Many severe asthma patients with high oral corticosteroid exposure (HOCS) often do not initiate biologics despite being eligible. This study aimed to compare the characteristics of severe asthma patients with HOCS who did and did not initiate biologics.

**Methods:** Baseline characteristics of patients with HOCS (long-term maintenance OCS therapy for at least 1 year, or  $\geq 4$  courses of steroid bursts in a year) from the International Severe Asthma Registry (ISAR; <https://isaregistries.org/>), who initiated or did not initiate biologics (anti-IgE, anti-IL5/5R or anti-IL4R), were described at the time of biologic initiation or registry enrolment. Statistical relationships were tested using Pearson's chi-squared tests for categorical variables, and t-tests for continuous variables, adjusting for potential errors in multiple comparisons.

**Results:** Between January 2015 and February 2021, we identified 1412 adult patients with severe asthma from 19 countries that met our inclusion criteria of HOCS, of whom 996 (70.5%) initiated a biologic and 416 (29.5%) did not. The frequency of biologic initiation varied across geographical regions. Those who initiated a biologic were more likely to have higher blood eosinophil count (483 vs 399 cells/ $\mu$ L,  $p=0.003$ ), serious infections (49.0% vs 13.3%,  $p<0.001$ ), nasal polyps (35.2% vs 23.6%,  $p<0.001$ ), airflow limitation (56.8% vs 51.8%,  $p=0.013$ ), and uncontrolled asthma (80.8% vs 73.2%,  $p=0.004$ ) despite greater conventional treatment adherence than those who did not start a biologic. Both groups had similar annual asthma exacerbation rates in the previous 12 months (5.7 vs 5.3,  $p=0.147$ ).

**Conclusion:** Around one third of severe HOCS asthma patients did not receive biologics despite a similar high burden of asthma exacerbations as those who initiated a biologic therapy. Other disease characteristics such as eosinophilic phenotype, serious infectious events, nasal polyps, airflow limitation and lack of asthma control appear to dictate biologic use.

**Keywords:** severe asthma, biologics, real-world, treatment pattern, patient characteristics

## Introduction

A major burden of severe asthma (SA) is the ongoing risk of severe exacerbations defined (according to the American Thoracic Society [ATS]/European Respiratory Society [ERS] Task Force) as a worsening of asthma which require use of oral corticosteroid (OCS) for at least 3 days, hospitalization, or emergency department (ED) visit.<sup>1</sup> The ongoing risk of recurrent severe exacerbations and other chronic daily symptoms lead to substantially increased healthcare resource use and costs and impaired quality of life<sup>2,3</sup> due to both acute care as well as the onset of various OCS-related side-effects and adverse outcomes.<sup>4,5</sup> OCS are commonly prescribed to treat or reduce the risk of inflammatory flare-ups after an asthma exacerbation (episodic use) or when asthma is still uncontrolled despite standard high-dose inhaled therapy (long-term maintenance use).<sup>6</sup> In Europe, 14–44% of all asthma patients studied used OCS, 6–9% were high OCS users (defined as OCS use of at least 450 mg prescribed in 3 months) at some point.<sup>7</sup> In the United States, the prevalence of OCS use is even higher: 65% of SA patients used OCS and 19% were classified as high OCS users, using the same definition.<sup>8</sup> In particular, long-term (maintenance) OCS is prevalent in approximately 20% to 60% of SA patients.<sup>9–11</sup>

In previous studies, the available therapeutic monoclonal antibodies (“biologics”, including omalizumab, mepolizumab, reslizumab, benralizumab and dupilumab) were found to reduce exacerbation frequency when used as add-on therapies to standard asthma therapies.<sup>12</sup> They can also improve asthma control and lung function, and some (mepolizumab, reslizumab, benralizumab and dupilumab) have shown OCS-sparing effects.<sup>12,13</sup> In a preliminary study of a large international SA cohort,<sup>11</sup> we have previously detected marked variability in the prescription criteria of biologics across country settings, assessed using the biologic accessibility score (BACS), a composite score incorporating 10 commonly used biologic eligibility criteria.<sup>14</sup> Referenced to European Medicines Agency marketing authorization specifications, a higher score reflected easier biologic access. The study found that for omalizumab, mepolizumab, benralizumab and dupilumab, only two, one, four and seven countries out of a total of 28, had equivalent or easier biologic access than that advocated by the EMA, and in all countries reslizumab was more difficult to access when compared to EMA eligibility criteria.<sup>14</sup> Biologic prescription criteria are informed by the strict inclusion/exclusion criteria in randomized controlled trials (RCTs) that show higher efficacy among T2-high patients, as well as differences in national prescribing criteria and reimbursement considerations. However, only about 10% of SA patients are eligible for enrollment in the Phase III trials, with a significant number of patients being excluded because of stipulations for airflow limitation, bronchodilator reversibility and smoking history.<sup>15</sup> For this reason, it is important to characterize SA patients with high oral corticosteroid exposure (HOCS) who were stepped up to a biologic therapy in real world settings. Precise profiling of these patients versus those who were not initiated on biologics will provide insight into this important segment of SA patients, enabling subsequent investigation into the real-world effects and cost-effectiveness of biologics in patients with HOCS.

Based on a large international cohort of SA patients with HOCS exposure, this study aims to identify the demographic and clinical features, including medication usage and co-morbidities, that are associated with those who were initiated on biologic therapy, compared to those who were not.

## Materials and Methods

### Study Design and Data Source

International Severe Asthma Registry (ISAR; <http://isaregistries.org/>), the largest adult SA registry in the world, and which is continually expanding, comprises de-identified, patient-level, longitudinal, real-life, standardized data from existing and newly created SA registries of 29 countries for over 10,000 patients.<sup>16–19</sup> For this study in particular, ISAR initially collected data for 5379 patients, using a core set of variables, from 19 countries (Argentina, Australia, Bulgaria, Canada, Colombia, Denmark, Greece, India, Ireland, Italy, Japan, Kuwait, Mexico, Saudi Arabia, South Korea, Spain, Taiwan, United Arab Emirates and the United Kingdom) between January 2015 and February 2021.<sup>18</sup> The ISAR database has ethical approval from the Anonymised Data Ethics Protocols and Transparency (ADEPT) committee (ADEPT0218). This study was designed, implemented, and reported in compliance with the European Network Centres for Pharmacoepidemiology and Pharmacovigilance Code of Conduct (EMA 2014; EUPAS33582) and with all applicable local and international laws and regulations.

### Study Cohort

This study included patients aged 18 years or older at enrolment and who have SA (ie receiving treatment at GINA 2018 Step 5 or with uncontrolled asthma at GINA Step 4).<sup>20</sup> A summary of how each registry diagnoses asthma and categorizes SA is provided in [Supplementary Table 1](#). In addition, patients in the study cohort were also required to have a history of HOCS exposure use for at least 12 months prior to the index date, defined as either having long-term (maintenance) use of OCS for at least 12 months prior, or using 4 or more courses of rescue steroid bursts for a 12-month period at baseline; a more strict definition than used in previous studies.<sup>7,8</sup> Patients who had received bronchial thermoplasty, any prior history of biologic use, or who had inadequate background data at the date of initiation, were excluded from the analysis.

The index date was defined as the date of biologic initiation for the *Biologic Initiated* group, assigned for those who received biologics (hereafter referred to as biologic initiators), and the date of ISAR enrolment for the *Biologic not Initiated group* (hereafter referred to as biologic non-initiators), assigned for those who never received biologics. The baseline period covers the 12 months prior to index date.

## Study Variables

Variables of interest included demographic variables (eg, age, age of asthma onset, gender, ethnicity, body mass index), smoking history, asthma duration, frequency of exacerbation, severity of exacerbation, asthma control status, positive testing for allergen tests, co-morbidities (OCS related and un-related), healthcare resource utilization (HCRU), biomarker concentrations (fractional exhaled nitric oxide [FeNO], total and specific serum IgE, and blood eosinophil count [BEC]), lung function, and treatment regimen. In addition, patients were also classified into different grades of eosinophilic phenotype likelihood, following a predefined eosinophilic asthma phenotype algorithm, based on highest BEC, long-term maintenance OCS use, elevated FeNO, presence of nasal polyps, and adult-onset of asthma.<sup>21</sup> A full description of variables collected is provided in [Supplementary Table 2](#) and [Supplementary Table 3](#). We also calculated the Biologic Accessibility Score (BACS) for different groups of biologics associated with each country, which incorporates ten access prescription criteria, reflecting that country's criteria to prescribe a particular biologic, and the "ease" of receiving the various biologics in asthma. A full description of the BACS index scores and the prescription criteria components are provided in [Supplementary Table 4](#).<sup>14</sup> Range of exacerbation counts is provided by counter in [Supplementary Table 5](#).

## Statistical Analyses

Descriptive statistics were computed for all demographic and clinical characteristics at baseline, based on whether they were continuous variables or categorical measures, as appropriate. These statistics were reported separately for those who did and did not initiate biologic therapy. Statistical relationships were tested using Pearson's chi-squared tests for categorical variables, and t-tests for continuous variables. To account for potential errors in multiple comparisons, we applied the robust Benjamini-Hochberg (B-H) procedure,<sup>22</sup> which calculated the critical p-value for significance in multiple testing, accepting up to 10% of false discovery rate. Statistical significance was defined as a p-value lower than the B-H critical p-value for multiple comparisons. Stata version 17 (College Station, TX, USA) was used to conduct all statistical analyses.

## Results

### Study Cohorts

Among 5379 prospective adult patients with SA from the 19 ISAR participating countries, 1412 were HOCS patients who met the inclusion criteria, as shown in [Figure 1](#). Of these, 996 (70.5%) initiated biologics and 416 (29.5%) did not. Of the biologic therapies, mepolizumab made up the majority (n=604, 62.7%; first available since 2015), followed by omalizumab (n=260; 27.0%; since 2003). A relatively smaller proportion of patients initiated benralizumab (n=82; 8.5%; since 2017), reslizumab (n=12, 1.2%; since 2016), or dupilumab (n=6; 0.6%; since 2016).

### Geographic Distribution

Geographical variation in the initiation of biologics was noted ([Figure 2](#)). However, there was no clear relationship between the proportion of patients who initiated biologics and the country-specific BACS scores.

### Demographic Characteristics ([Table 1](#))

Mean age and BMI were similar across biologic initiated and non-initiated groups (age, 51.7 vs 53.2 years, p=0.08; BMI, 29.3 vs 29.7 kg/m<sup>2</sup>, p=0.28). However, compared to those who did not initiate biologics, biologic initiators were more likely to be Caucasian (77.7% vs 65.1%, p<0.001).

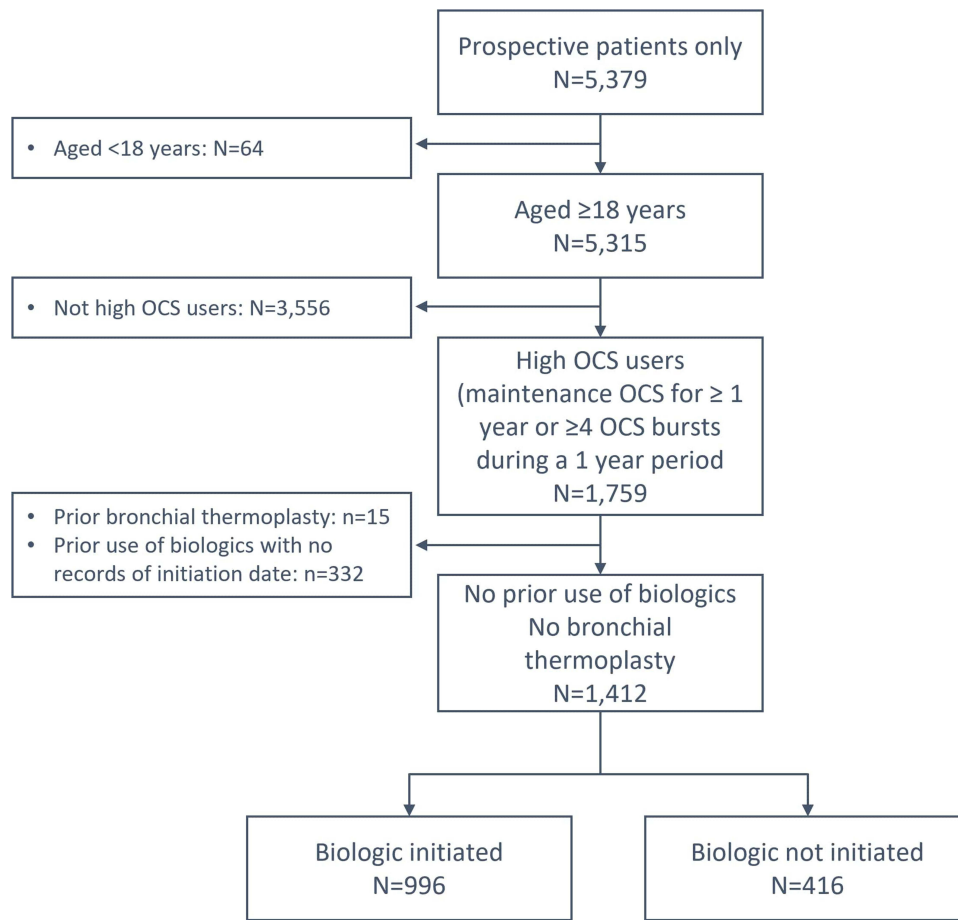


Figure 1 Flowchart of cohort creation.

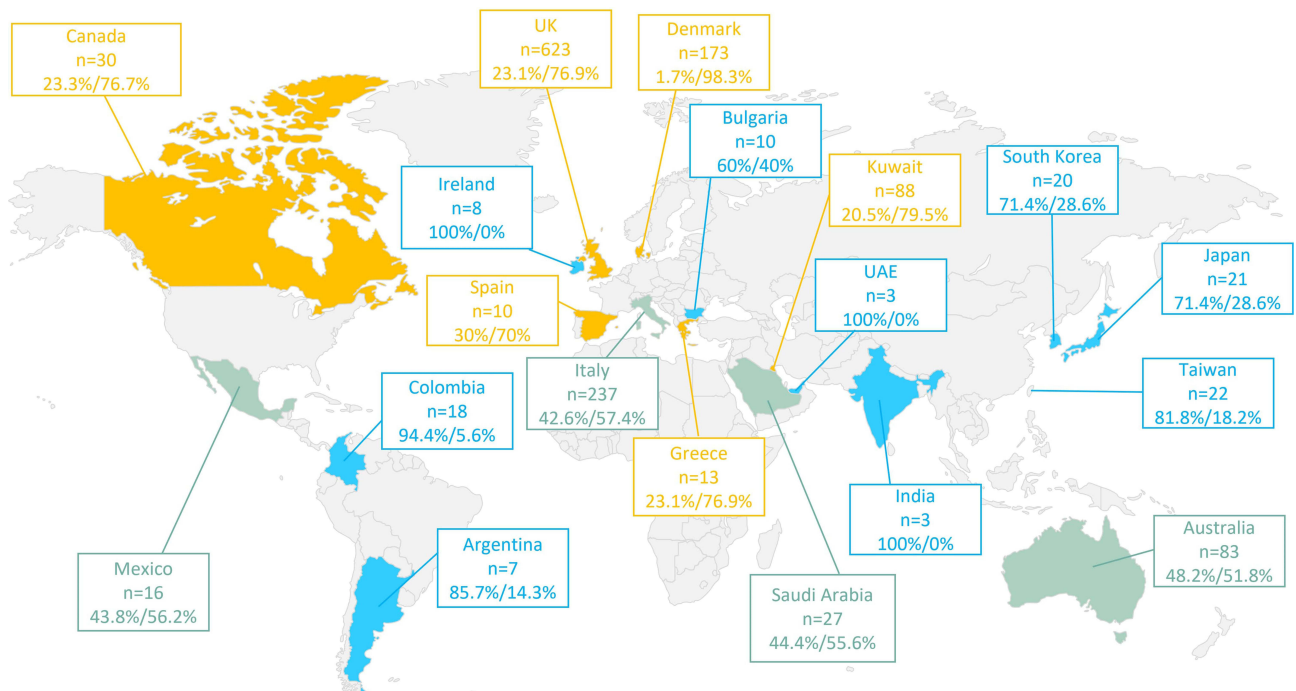


Figure 2 Geographic distribution of adult severe asthma patients with high oral corticosteroid exposure enrolled in ISAR according to biologic initiation status. ISAR: International Severe Asthma Registry. Data are presented as % not initiated/% initiated. Green: approximately equal proportion of biologic non-initiators to initiators; Blue: More likely not to initiate biologics; Yellow: more likely to initiate biologics.



**Table 1** Baseline Demographic Characteristics for ISAR Patients with Severe Asthma and High Oral Corticosteroid Exposure Who Were and Were Not Initiated on Biologic (Bx) Therapy

	<b>BX Not Initiated</b>	<b>BX Initiated</b>	<b>P-value</b>	<b>B-H Critical P value Threshold for Significance in Multiple Testing</b>
Age, yrs Mean (SD)	n = 416 53.2 (14.5)	n = 996 51.7 (13.9)	0.075	
18–34, n (%)	50 (12.0)	131 (13.2)	0.010	0.028
35–54, n (%)	153 (36.8)	418 (42.0)		
55–79, n (%)	203 (48.8)	440 (44.2)		
80+, n (%)	10 (2.4)	7 (0.7)		
Gender Female, n (%)	n = 416 277 (66.6)	n = 996 609 (61.1)	0.050	0.040
Race/Ethnicity	n = 375	n = 887	<0.001	0.007
Caucasian, n (%)	244 (65.1)	689 (77.7)		
Asian, n (%)	65 (17.3)	62 (7.0)		
African, n (%)	10 (2.7)	36 (4.1)		
Mixed, n (%)	1 (0.3)	17 (1.9)		
Other†, n (%)	55 (14.7)	83 (9.4)		
BMI Category, Kg/m <sup>2</sup> Mean (SD)	n = 410 29.7 (7.7)	n = 960 29.3 (6.8)	0.280	0.066
Underweight (BMI <18.5), n (%)	11 (2.7)	13 (1.4)	0.310	0.071
Normal (BMI 18.5 to <25), n (%)	106 (25.9)	264 (27.5)		
Overweight (BMI 25 to <30), n (%)	126 (30.7)	309 (32.2)		
Obese (BMI ≥30), n (%)	167 (40.7)	374 (39.0)		
Tobacco smoking status †	n = 410	n = 936	0.010	0.029
Current smoker, n (%)	23 (5.6)	23 (2.5)		
Ex-smoker, n (%)	106 (25.9)	267 (28.5)		
Non-smoker, n (%)	281 (68.5)	646 (69.0)		
Tobacco smoking pack-years† Mean (SD)	n = 117 15.25 (16.31)	n = 249 18.97 (17.62)	0.050	0.041
<6, n (%)	41 (35.0)	56 (22.5)	0.011	0.033
≥6, n (%)	76 (65.0)	193 (77.5)		
≤10, n (%)	67 (57.3)	105 (42.2)	0.007	0.021
>10, n (%)	50 (42.7)	144 (57.8)		

**Notes:** †does not include hookah smoking. Test statistics: Pearson Chi Square test for categorical variables with > 2 categories, McNemar's test for categorical variables with 2 categories and T-test for continuous variables.

**Abbreviations:** B-H, Benjamini-Hochberg Procedure; BMI, body mass index; ISAR, International Severe Asthma Registry; SD, standard deviation.

## Clinical Characteristics (Table 2 and Figure 3)

### Asthma Status

Biologic initiators were comparable to non-initiators with regard to age of onset of asthma (year, 27.9 vs 29.5,  $p=0.15$ ), duration of asthma (year, 23.7 vs 23.8,  $p=0.91$ ), and number of asthma exacerbations over the past year (5.7 vs 5.3,  $p=0.15$ ). However, patients who initiated biologics were more likely to have uncontrolled asthma (80.8% vs 73.2%,  $p=0.004$ ) as defined by either GINA criteria, Asthma Control Questionnaire or Asthma Control Test, as well as better treatment adherence as defined by a mix of setting-specific methods (88.7% vs 76.2%,  $p<0.001$ ), compared to those who did not initiate biologics.

**Table 2** Baseline Clinical Characteristics for ISAR Patients with Severe Asthma and High Oral Corticosteroid Exposure Who Were and Were Not Initiated on Biologic (Bx) Therapy

	<b>BX Not Initiated</b>	<b>BX Initiated</b>	<b>P-value</b>	<b>B-H Critical P value Threshold for Significance in Multiple Testing</b>
Age of asthma onset Mean (SD)	N=402 29.5 (18.7)	N=876 27.9 (18.7)	0.150	0.057
Asthma duration Mean (SD)	N=394 23.8 (16.3)	N=859 23.7 (16.7)	0.910	0.098
Asthma control*	N=381	N=777	0.004	0.017
Controlled, n (%)	26 (6.8)	51 (6.6)		
Partially controlled, n (%)	76 (20.0)	98 (12.6)		
Uncontrolled, n (%)	279 (73.2)	628 (80.8)		
No. asthma exacerbations in the past year (excluding cases with 0 exacerbations) Mean (SD)	N=334 5.3 (4.0)	N=849 5.7 (3.9)	0.147	0.055
1, n (%)	26 (7.8)	75 (8.8)	0.009	0.024
2, n (%)	39 (11.7)	82 (9.7)		
3, n (%)	28 (8.4)	61 (7.2)		
4, n (%)	85 (25.5)	181 (21.3)		
5, n (%)	60 (18.0)	112 (13.2)		
≥6, n (%)	96 (28.7)	338 (39.8)		
Adherence*	N=327	N=873		
Adherent, n (%)	249 (76.2)	774 (88.7)	<0.001	0.002
Poor: Clinical impression, n (%)	25 (7.7)	12 (1.4)		
Poor: Prescription records, n (%)	53 (16.2)	87 (10.0)		
<b>Positive allergen test</b>				
Serum specific IgE test to allergens Positive, n (%)	N=340 112 (32.9)	N=926 396 (42.8)	0.002	0.012
Skin prick test to allergens Positive, n (%)	N=340 99 (29.1)	N=926 305 (32.9)	0.196	0.060
<b>Healthcare resource utilization</b>				
Emergency department visit, N (%)	N=416 157 (37.7)	N=996 321 (32.2)	0.046	0.038
Hospital admission, N (%)	131 (31.5)	286 (28.7)	0.297	0.069
Invasive ventilation (ever), N (%)	27 (6.5)	69 (6.9)	0.766	0.088
<b>Post-bronchodilator (BD) lung function</b>				
Post-BD FEV <sub>1</sub> , % predicted Mean (SD)	N=296 72.69 (23.29)	N=840 73.09 (34.59)	0.854	0.091
Post-BD FEV <sub>1</sub> /FVC Mean (SD)	N=282 0.71 (0.18)	N=826 0.67 (0.22)	0.008	0.022
Post-BD FEV <sub>1</sub> /FVC < 0.7, n (%)	N=282 136 (51.8)	N=826 469 (56.8)	0.013	0.034

(Continued)

Table 2 (Continued).

	BX Not Initiated	BX Initiated	P-value	B-H Critical P value Threshold for Significance in Multiple Testing
<b>Biomarkers</b>				
Serum total IgE, IU (mL)	N=313	N=882	0.055	0.045
<150, n (%)	165 (52.7)	396 (44.9)		
150–400, n (%)	67 (21.4)	229 (26.0)		
>400, n (%)	81 (25.9)	257 (29.1)		
BEC (μL)	N=329	N=919	0.003	0.014
Highest, Mean (SD)	398.9 (371.4)	482.8 (468.7)		
150, n (%)	88 (26.8)	220 (23.9)		
>150 to ≤ 300, n (%)	90 (27.4)	220 (23.9)		
>300 to ≤ 450, n (%)	43 (13.1)	99 (10.8)		
>450, n (%)	108 (32.8)	380 (41.4)	0.057	0.047
FeNO, ppb	N=218	N=701	0.010	0.031
<25, n (%)	87 (39.9)	205 (29.2)		
25–50, n (%)	53 (24.3)	220 (31.4)		
>50, n (%)	78 (35.8)	276 (39.4)		
Low T2 biomarker, n (%)	N=183	N=666	0.003	0.016
	30 (16.4)	58 (8.7)		
High T2 biomarker, n (%)	N=183	N=666	0.742	0.086
	75 (41.0)	282 (42.3)		
ISAR gradient eosinophilic phenotype	N=325	N=911	<0.001	0.003
Grade 0 (unlikely), n (%)	7 (2.2)	2 (0.2)		
Grade 1 (least likely), n (%)	35 (10.8)	20 (2.2)		
Grade 2 (Likely), n (%)	62 (19.1)	62 (6.8)		
Grade 3 (most likely), n (%)	221 (68.0)	827 (90.8)		
<b>Co-morbidities</b>				
Potential OCS-related co-morbidities				
Anxiety, n (%)	N=230	N=260	0.906	0.097
	31 (13.5)	36 (13.9)		
Depression, n (%)	N=227	N=254	0.474	0.079
	25 (11.0)	23 (9.1)		
Osteoporosis, n (%)	N=304	N=611	0.009	0.026
	52 (17.1)	67 (11.0)		
Peptic ulcer, n (%)	N=185	N=205	0.218	0.062
	10 (5.4)	6 (2.9)		
Type II diabetes, n (%)	N=170	N=210	0.239	0.064
	31 (18.2)	29 (13.8)		
History of Pneumonia, n (%)	N=184	N=205	0.900	0.095
	15 (8.2)	16 (7.8)		
Cataract, n (%)	N=128	N=108	0.437	0.076
	9 (7.0)	5 (4.6)		
Embolicism, n (%)	N=126	N=105	0.854	0.093
	2 (1.6)	2 (1.9)		

(Continued)



Table 2 (Continued).

	BX Not Initiated	BX Initiated	P-value	B-H Critical P value Threshold for Significance in Multiple Testing
Glaucoma, n (%)	N=128 2 (1.6)	N=108 5 (4.6)	0.166	0.059
Heart failure, n (%)	N=128 3 (2.3)	N=104 1 (1.0)	0.421	0.074
Myocardial infarction, n (%)	N=166 3 (1.8)	N=148 5 (3.4)	0.378	0.072
Renal failure, n (%)	N=185 2 (1.1)	N=205 0 (0.0)	0.136	0.053
Sleep apnea, n (%)	N=173 29 (16.8)	N=231 35 (15.2)	0.661	0.081
Stroke, n (%)	N=166 0 (0.0)	N=146 1 (0.7)	0.286	0.067
<b>T2 Comorbidities (ever)</b>				
Allergic rhinitis, n (%)	N=416 168 (40.4)	N=996 313 (31.4)	0.001	0.010
Chronic rhinosinusitis, n (%)	83 (20.0)	246 (24.7)	0.054	0.043
Eczema, n (%)	38 (9.1)	98 (9.8)	0.682	0.084
Nasal polyps, n (%)	98 (23.6)	351 (35.2)	<0.001	0.005
<b>Other</b>				
Anaphylaxis event, n (%)	N=197 5 (2.5)	N=399 2 (0.5)	0.030	0.036
Cancer event, n (%)	N=199 13 (6.5)	N=393 8 (2.0)	0.005	0.019
Serious infection event, n (%)	N=196 26 (13.3)	N=396 194 (49.0)	<0.001	0.009
<b>Asthma therapy</b>				
Add-on treatment to ICS/LABA	N=416	N=996		
Long term OCS, n (%)†	247 (59.4)	612 (61.5)	0.467	0.078
LTRA, n (%)	181 (43.5)	427 (42.9)	0.825	0.090
Long-term macrolide, n (%)	25 (6.0)	54 (5.4)	0.661	0.083
Steroid-sparing, n (%)	8 (1.9)	8 (0.8)	0.070	0.050
Theophylline, n (%)	64 (15.4)	169 (17.0)	0.465	0.100
LAMA, n(%)	216 (51.9)	463 (46.5)	0.062	0.048

**Notes:** \*Treatment adherence was evaluated through a mix of methods in different countries in ISAR registry. †LTOCS: OCS therapy for at least 3 months.

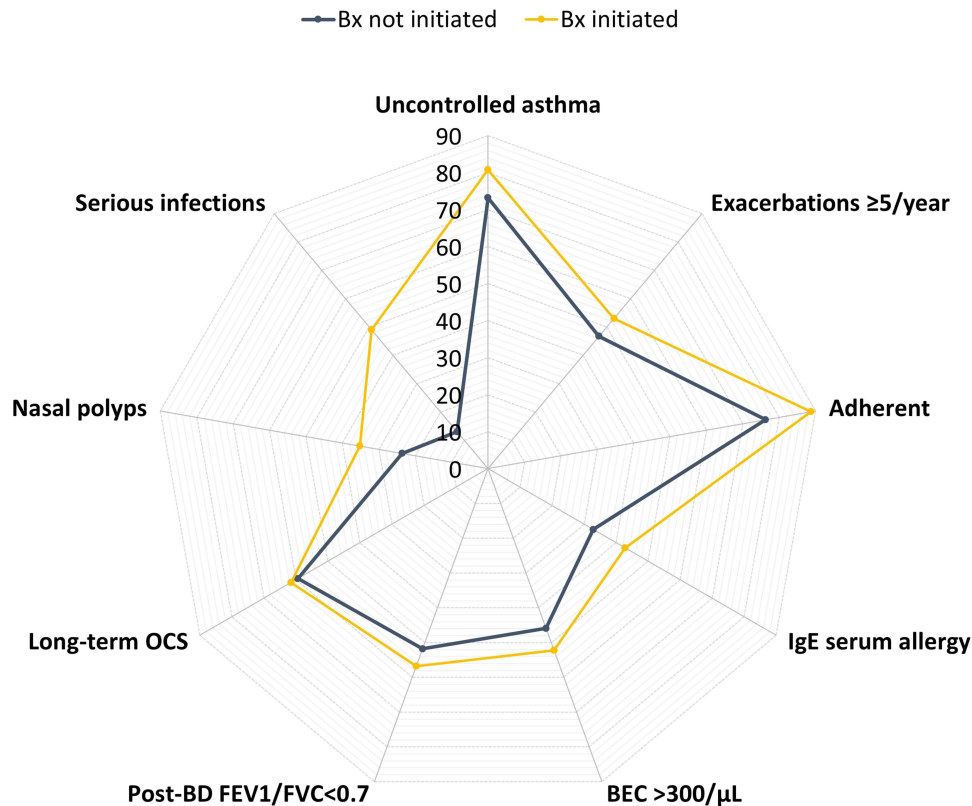
**Abbreviations:** BEC, blood eosinophil count; B-H, Benjamini-Hochberg Procedure; FeNO, fractional exhaled nitric oxide; FEV<sub>1</sub>, forced expiratory volume in one second; FVC, forced vital capacity; GINA, Global Initiative for Asthma; ICS, inhaled corticosteroid; IgE, Immunoglobulin E; ISAR, International Severe Asthma Registry; LABA, long-acting  $\beta_2$ -agonist; LAMA, long-acting muscarinic; LTRA, leukotriene receptor antagonist; OCS, oral corticosteroid; SD, standard deviation.

## Lung Function

Patients who initiated biologics had similar post-bronchodilator FEV<sub>1</sub> as a percentage of predicted FEV<sub>1</sub> (73.1% vs 72.7%, p=0.85), and a modestly greater degree of airflow limitation according to the proportion with a FEV<sub>1</sub>/FVC ratio of less than 0.7 (56.8% vs 51.8%, p=0.013), compared to non-initiators.

## Eosinophilic Asthma

Patients who initiated biologics also had a higher mean BEC (483/ $\mu$ L vs 399/ $\mu$ L, p=0.003), slightly higher FeNO concentrations (25–50 ppb, 31.4% vs 24.3%; >50 ppb, 39.4% vs 35.8%, p=0.010), and were more likely to be of ISAR Grade 3 eosinophilic phenotype (90.8% vs 68.0%, p<0.001), compared to non-initiators. Of note, there were fewer



**Figure 3** Clinical characteristics of adult severe asthma patients with high oral corticosteroid exposure enrolled in ISAR who did and did not initiate biologic therapy. **Abbreviations:** BEC, blood eosinophil count; BD, bronchodilator; Bx, biologic; FEV<sub>1</sub>, forced expiratory volume in one second; FVC, forced vital capacity; IgE, immunoglobulin E; ISAR, International Severe Asthma Registry; OCS, oral corticosteroid.

biologic initiators with low T2 biomarkers compared to non-initiators (8.7% vs 16.4%,  $p=0.003$ ), defined as  $\text{BEC} < 150/\mu\text{L}$  and  $\text{FeNO} < 25\text{ppb}$ . However, the proportion of high T2 biomarkers were similar between biologic initiators and non-initiators (42.3% vs 41.0%,  $p=0.742$ ), defined as  $\text{BEC} \geq 300/\mu\text{L}$  and  $\text{FeNO} \geq 30\text{ppb}$ .

### Allergic Asthma

Similar proportions of patients tested positive for skin prick allergen tests (32.9% vs 29.1%,  $p=0.20$ ), but more biologic initiators had a positive serum allergen test (42.8% vs 32.9%,  $p=0.002$ ) compared to non-initiators.

### Current Medication and Comorbidities

The distribution of ICS/LABA add-on therapies and most co-morbidities were similar across groups. However, patients who initiated biologics were less likely to have osteoporosis (11.0% vs 17.1%,  $p=0.009$ ), allergic rhinitis (31.4% vs 40.4%,  $p=0.001$ ), cancer (2.0% vs 6.5%,  $p=0.005$ ), and anaphylaxis (0.5% vs 2.5%,  $p=0.030$ ), compared to non-initiators. On the other hand, biologic initiators were more likely to have a serious infection, defined as an infection that required hospitalization, invasive or non-invasive ventilation, IV antibiotics, or that resulted in a fatal outcome (49.0% vs 13.3%,  $p<0.001$ ), and were also more likely to have nasal polyps (35.2% vs 23.6%,  $p<0.001$ ).

### Health Services Use in the Past Year

Both biologic initiators and non-initiators had similar proportions of patients with hospital admissions (28.7% vs 31.5%,  $p=0.30$ ) and ICU admissions involving use of invasive ventilations (6.9% vs 6.5%,  $p=0.77$ ). Although biologic initiators tended to have a lower proportion of patients with emergency department visits (32.2% vs 37.7%), the difference did not reach significance after the B-H adjustment for multiple comparison errors ( $p$ -value of 0.046 > B-H significance threshold of 0.038).

## Discussion

In the ISAR cohort, the initiation of biologic therapies varied across countries. Nearly one third of SA patients with HOCS did not receive biologics, but these patients had similarly high frequencies of asthma exacerbation and HCRU as biologic initiators, suggesting that exacerbation history was not driving biologic prescription even though it is an important prescription criterion in many countries.<sup>14</sup> On the other hand, eosinophilic asthma defined in terms of elevated biomarkers for airway inflammation (eg, BEC, nasal polyps), uncontrolled asthma despite treatment adherence, and airway limitation, as well as other co-morbidities that often accompany severe disease such as the occurrence of serious infection, appeared to be potential decision determinants for biologic initiation. The use of both endotype and phenotype biomarkers to direct biologic prescription decisions is in line with a precision medicine-based approach, and the 2021 GINA strategy recommendations.<sup>23</sup>

The decision to initiate biologics exhibited a clear geographic pattern. For instance, SA patients with HOCS in UK, Denmark, Italy and Kuwait were more likely to initiate biologics than not. This pattern was related to country-income level (Eg, East Asia versus Middle East and developed countries versus low-to-middle income countries). Others have found that higher income level and better insurance coverage are associated with biologic initiation.<sup>24</sup> There was also noticeable inconsistency between the initiation of biologics and country-specific biologic accessibility, suggesting that prescription criteria, and by extension, biologic accessibility, were not the sole determinants for biologic initiation in certain countries. Moreover, as a number of biologics only became available in 2015 and 2016, and our data were retrieved from 2015 to 2021, the lack of biologic availability may have hindered biologic initiation in some countries.

Our finding that a considerable portion (29%) of SA patients with HOCS did not receive biologics was in agreement with a recent ISAR publication, which showed that 51.1% of patients with SA (but not necessarily HOCS) received regular intermittent OCS, whereas only 25.4% were on biologics.<sup>11</sup> Although long-term OCS use is associated with numerous adverse health outcomes,<sup>4,5</sup> greatly increased healthcare costs and impaired quality of life,<sup>2,3</sup> biologics such as mepolizumab, benralizumab and dupilumab have demonstrated steroid sparing effect in large clinical trials.<sup>25–27</sup> Considering the further benefits of biologics in reducing the burden of asthma exacerbations, our finding highlights the need to weigh up the potential harms of long-term OCS use with the benefits of biologics when considering the treatment of severe asthma.

Interestingly, exacerbation frequency and HCRU did not appear to increase the likelihood of biologic initiation in our cohort of SA patients; a surprising finding when bearing in mind that these patients in both groups were on HOCS but still experienced on average more than 5 exacerbations in the prior year, and that a history of exacerbation is a prerequisite of biologic use according to both biologic indications and country-specific eligibility criteria.<sup>14</sup> A recent international study by Porsbjerg and colleagues found that approximately half of the 28 countries included required two or more severe exacerbations in the previous year (ie, exacerbations that require treatment with OCS or led to ED visit and/or hospitalization) for a biologic prescription.<sup>14</sup> Indeed, ‘frequent exacerbators’ are increasingly recognized as an important subgroup for targeted therapy, because these patients account for a disproportionately high proportion of the total asthma exacerbation burden, with frequent exacerbations associated with greatly increased risk of adverse health events and compromised quality of life.<sup>13</sup> Recent studies have found that ‘frequent exacerbators’ have the most room for improvement<sup>28–30</sup> and so should be particularly considered for biologics.<sup>13</sup>

Over 40% of SA HOCS patients were with high T2 biomarkers regardless of whether a biologic was initiated. Nonetheless, our study further showed that the initiation of biologic therapy was more likely in those with greater degree of eosinophilic asthma (indicated by higher baseline BEC and greater prevalence of nasal polyps in the biologic initiator group), which was in agreement with recent studies from both the US<sup>24</sup> and UK.<sup>31</sup> Use of BEC as a criterion for biologic initiation aligns with country-specific biologic eligibility criteria,<sup>14</sup> and is likely informed by the positive correlation between higher BEC and better biologic response.<sup>32</sup> Similarly, the greater likelihood of biologic initiation in patients with nasal polyps is likely due to the greater exacerbation frequency seen in SA patients with nasal polyps, more OCS bursts, a greater reduction of exacerbation burden on biologics in these patients,<sup>33</sup> and the fact that omalizumab, mepolizumab and dupilumab are also indicated for the treatment of nasal polyps.<sup>34</sup> In addition, the much higher frequency of severe infectious events in biologic initiators might be another trigger for physicians to initiate biologics,<sup>35</sup> because viral respiratory infections are a major cause of asthma exacerbations.<sup>36</sup>

We found no significant difference between biologic initiators and non-initiators with regard to asthma therapy at baseline. Although patients who initiated biologics were more likely to be fully adherent to their treatment regimen compared to those who did not initiate biologics, they were also more likely to have uncontrolled asthma. A recent ISAR study on global biologic accessibility found that between 43% and 60% of countries surveyed did not require or had not decided on adherence as a criterion for biologic eligibility.<sup>14</sup> However, a large systematic review reported that nearly 70% of mepolizumab users with SA have good ICS adherence before and on mepolizumab, while good ICS adherence is associated with greater reductions in OCS dose and exacerbations.<sup>37</sup> On the contrary, low adherence to OCS was reported in roughly 40% of SA patients in the U-BIOPRED cohort.<sup>38</sup> Of note, treatment adherence was defined by prescription records and clinical impressions, which varied by settings of ISAR cohort. Regardless of subjective or objective measures, the findings that biologic initiators have more uncontrolled asthma and mostly full treatment adherence to ICS was in line with GINA recommendations.<sup>23</sup>

This study has several limitations. First, given its observational nature, recall bias was almost inevitable. Second, other factors such as biologic affordability, insurance coverage administrative burdens, and government reimbursement criteria (all of which are country specific) likely influenced the decision to initiate biologics. Future research to investigate physician reasons to prescribe and not prescribe biologics is warranted. In addition, there was also potential for confounding by country (eg, the UK was over-represented in the biologic initiator group which may have skewed findings) and, like with other registries, patients may not have been truly representative of the real-life asthma population (albeit more representative than RCT populations). Notwithstanding these limitations, we are confident of the representativeness of the ISAR population as the vast majority of severe asthma patients included in all asthma specialist centres elected to participate in ISAR, or else data were collected directly from EMR embedded registries. A major strength of this study is its size, including a more heterogeneous population than that included in randomized controlled trials, with greater generalizability to real life. The global coverage of ISAR, including standardized data from 19 countries, enabled us to explore the clinical characteristics driving initiation of biologics in everyday clinical practice. Our study cohort possessed an extensive collection of clinical information, social and health determinants, enabling a thorough investigation of patient characteristics and a longitudinal follow-up for risk prediction modelling and/or comparative effectiveness study of biologic initiation.

## Conclusions

Eosinophilic phenotype, serious infectious events, nasal polyps, airflow limitation and inadequate asthma control appear to encourage physicians to prescribe biologic therapy for SA patients with HOCS in real life. On the other hand, one third of severe HOCS asthma patients did not receive biologics despite similar exacerbation frequency and HCRU as those who initiated a biologic therapy. These findings suggest the need to consider multiple characteristics to guide the initiation of biologics in SA patients, which will optimize efficiency and cost-effectiveness.<sup>39–41</sup> Future research should include a rigorous method to ensure comparability of the treatment arms, such as propensity scores, to assess the real-world effectiveness of biologics over time in SA patients with HOCS. In addition, we need to develop an individualized treatment algorithm to guide the initiation of biologics. The ISAR cohort could be suitable for both of these studies.

## Ethics Approval

This study was designed, implemented, and reported in compliance with the European Network Centres for Pharmacoepidemiology and Pharmacovigilance Code of Conduct (EMA 2014; EUPAS33582) and with all applicable local and international laws and regulation. Registration of the ISAR database with the European Union Electronic Register of Post-Authorization studies was also undertaken (ENCEPP/DSPP/23720). ISAR has ethical approval from the Anonymised Data Ethics Protocols and Transparency (ADEPT) committee (ADEPT0218). Governance was provided by The Anonymous Data Ethics Protocols and Transparency (ADEPT) committee (registration number: ADEPT0420). All data collection sites in the International Severe Asthma Registry (ISAR) have obtained regulatory agreement in compliance with specific data transfer laws, country-specific legislation, and relevant ethical boards and organizations.

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  - Concord Hospital, NSW
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  - Flinders Medical Centre, SA
  - Frankston Hospital, VIC
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- Ulsan University Hospital
- Haeundae Paik Hospital
- Hallym University Chuncheon Sacred Heart Hospital
- Hanyang University Hospital
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  - King Fahad Medical City, Riyadh
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## 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. The study was supervised by David B. Price.

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Enrico Heffler participates in speaking activities and industry advisory committees for AstraZeneca, Sanofi-Genzyme, GSK, Novartis, Regeneron, Stallergenes-Greer, TEVA, Circassia and Nestlé Purina, grants from AstraZeneca and GSK

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## References

1. Reddel HK, Taylor DR, Bateman ED., et al. An official American Thoracic Society/European Respiratory Society statement: asthma control and exacerbations: standardizing endpoints for clinical asthma trials and clinical practice. *Am J Respir Crit Care Med.* 2009;180:59–99. doi:10.1164/rccm.200801-060ST
2. Luskin AT, Antonova EN, Broder MS, et al. Health care resource use and costs associated with possible side effects of high oral corticosteroid use in asthma: a claims-based analysis. *Clinicoecon Outcomes Res.* 2016;8:641–648. doi:10.2147/CEOR.S115025
3. Canonica GW, Colombo GL, Bruno GM, et al. Shadow cost of oral corticosteroids-related adverse events: a pharmacoeconomic evaluation applied to real-life data from the Severe Asthma Network in Italy (SANI) registry. *World Allergy Org J.* 2019;12:100007. doi:10.1016/j.waojou.2018.12.001
4. Price DB, Trudo F, Voorham J, et al. Adverse outcomes from initiation of systemic corticosteroids for asthma: long-term observational study. *J Asthma Allergy.* 2018;11:193–204. doi:10.2147/JAA.S176026
5. Sweeney J, Patterson CC, Menzies-Gow A, et al. Comorbidity in severe asthma requiring systemic corticosteroid therapy: cross-sectional data from the Optimum Patient Care Research Database and the British Thoracic Difficult Asthma Registry. *Thorax.* 2016;71:339–346. doi:10.1136/thoraxjnl-2015-207630
6. Fardet L, Petersen I, Nazareth I. Prevalence of long-term oral glucocorticoid prescriptions in the UK over the past 20 years. *Rheumatology.* 2011;50:1982–1990. doi:10.1093/rheumatology/ker017
7. Tran TN, King E, Sarkar R, et al. Oral Corticosteroid Prescription Patterns for Asthma in France, Germany, Italy, and the United Kingdom. *Eur Respir J.* 2020. doi:10.1183/13993003.02363-2019
8. Tran TN, MacLachlan S, Hicks W, et al. Oral Corticosteroid Treatment Patterns of Patients in the United States with Persistent Asthma. *J Allergy Clin Immunol Pract.* 2021;9:338–346.e3. doi:10.1016/j.jaip.2020.06.019
9. Bleecker ER, Menzies-Gow AN, Price DB, et al. Systematic Literature Review of Systemic Corticosteroid Use for Asthma Management. *Am J Respir Crit Care Med.* 2020;201:276–293. doi:10.1164/rccm.201904-0903SO
10. Voorham J, Xu X, Price DB, et al. Healthcare resource utilization and costs associated with incremental systemic corticosteroid exposure in asthma. *Allergy.* 2019;74:273–283. doi:10.1111/all.13556
11. Wang E, Wechsler ME, Tran TN, et al. Characterization of Severe Asthma Worldwide: data From the International Severe Asthma Registry. *Chest.* 2020;157:790–804. doi:10.1016/j.chest.2019.10.053
12. Agache I, Beltran J, Akdis C, et al. Efficacy and safety of treatment with biologicals (benralizumab, dupilumab, mepolizumab, omalizumab and reslizumab) for severe eosinophilic asthma. A systematic review for the EAACI Guidelines - recommendations on the use of biologicals in severe asthma. *Allergy.* 2020;75:1023–1042. doi:10.1111/all.14221
13. Krings JG, McGregor MC, Bacharier LB, et al. Biologics for Severe Asthma: treatment-Specific Effects Are Important in Choosing a Specific Agent. *J Allergy Clin Immunol.* 2019;7:1379–1392. doi:10.1016/j.jaip.2019.03.008
14. 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;10:1202–1216. doi:10.1016/j.jaip.2021.12.027
15. Brown T, Jones T, Gove K, et al. Randomised controlled trials in severe asthma: selection by phenotype or stereotype. *Eur Respir J.* 2018;52. doi:10.1183/13993003.01444-2018
16. 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.
17. Bulathsinghala L, Eleangovan N, Heaney LG, et al. Development of the International Severe Asthma Registry (ISAR): a Modified Delphi Study. *J Allergy Clin Immunol Pract.* 2019;7:578–588.e2. doi:10.1016/j.jaip.2018.08.016
18. ISAR Study Group. International Severe Asthma Registry (ISAR): mission Statement. *Chest.* 2020;157:805–814.



19. Wang E, Wechsler ME, Tran TN, et al. Characterization of severe asthma worldwide: data from the International Severe Asthma Registry (ISAR). *Chest*. 2020;157:805–814.
20. Global Initiative for Chronic Obstructive Lung Disease. Global Strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease; 2018. Available from: [https://goldcopd.org/wp-content/uploads/2017/11/GOLD-2018-v6.0-FINAL-revised-20-Nov\\_WMS.pdf](https://goldcopd.org/wp-content/uploads/2017/11/GOLD-2018-v6.0-FINAL-revised-20-Nov_WMS.pdf). Accessed September 28, 2022.
21. Heaney LG. Eosinophilic and Noneosinophilic Asthma: an Expert Consensus Framework to Characterize Phenotypes in a Global Real-Life Severe Asthma Cohort. *CHEST*. 2021. doi:10.1016/j.chest.2021.04.013
22. Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. *J Royal Statistical Soc Series B*. 1995;57:289–300.
23. Reddel HK, Bacharier LB, Bateman ED, et al. Global Initiative for Asthma (GINA) Strategy 2021 - Executive summary and rationale for key changes. *Eur Respir J*. 2021. doi:10.1183/13993003.02730-2021
24. Inselman JW, Jeffery MM, Maddux JT, et al. Trends and Disparities in Asthma Biologic Use in the United States. *J Allergy Clin Immunol Pract*. 2020;8:549–554.e1. doi:10.1016/j.jaip.2019.08.024
25. Bel EH, Wenzel SE, Thompson PJ, et al. Oral Glucocorticoid-Sparing Effect of Mepolizumab in Eosinophilic Asthma. *N Eng J Med*. 2014;371:1189–1197. doi:10.1056/NEJMoa1403291
26. Nair P, Wenzel S, Rabe KF, et al. Oral Glucocorticoid-Sparing Effect of Benralizumab in Severe Asthma. *N Eng J Med*. 2017;376:2448–2458. doi:10.1056/NEJMoa1703501
27. Rabe KF, Nair P, Brusselle G, et al. Efficacy and Safety of Dupilumab in Glucocorticoid-Dependent Severe Asthma. *N Eng J Med*. 2018;378:2475–2485. doi:10.1056/NEJMoa1804093
28. FitzGerald JM, Bleecker ER, Nair P, et al. Benralizumab, an anti-interleukin-5 receptor  $\alpha$  monoclonal antibody, as add-on treatment for patients with severe, uncontrolled, eosinophilic asthma (CALIMA): a randomised, double-blind, placebo-controlled Phase 3 trial. *Lancet*. 2016;388:2128–2141. doi:10.1016/S0140-6736(16)
29. Castro M, Zangrilli J, Wechsler ME, et al. Reslizumab for inadequately controlled asthma with elevated blood eosinophil counts: results from two multicentre, parallel, double-blind, randomised, placebo-controlled, phase 3 trials. *Lancet Respir Med*. 2015;3:355–366. doi:10.1016/S2213-2600(15)
30. Pavord ID, Korn S, Howarth P, et al. Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial. *Lancet*. 2012;380:651–659. doi:10.1016/S0140-6736(12)
31. 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;76:220–227. doi:10.1136/thoraxjnl-2020-215168
32. Ortega H, Gleich G, Mayer B, et al. Reproducibility of a Single Blood Eosinophil Measurement as a Biomarker in Severe Eosinophilic Asthma. *Annals ATS*. 2015;12:1896–1897. doi:10.1513/AnnalsATS.201507-443LE
33. Tinoco EM, Gigante AR, Fernandes AL, et al. Impact of biologic therapy in severe asthma with nasal polyps. *Eur Respir J*. 2021;58. doi:10.1183/13993003.congress-2021.PA3739
34. Bachert C, Han JK, Desrosiers M, et al. Efficacy and safety of dupilumab in patients with severe chronic rhinosinusitis with nasal polyps (LIBERTY NP SINUS-24 and LIBERTY NP SINUS-52): results from two multicentre, randomised, double-blind, placebo-controlled, parallel-group phase 3 trials. *Lancet*. 2019;394:1638–1650. doi:10.1016/S0140-6736(19)
35. Rogliani P, Calzetta L, Matera MG, et al. Severe Asthma and Biological Therapy: when, Which, and for Whom. *Pulm Ther*. 2020;6:47–66. doi:10.1007/s41030-019-00109-1
36. Matera MG, Calzetta L, Sanduzzi A, et al. Effects of neuraminidase on equine isolated bronchi. *Pulm Pharmacol Ther*. 2008;21:624–629. doi:10.1016/j.pupt.2008.02.003
37. d'Ancona G, Kavanagh J, Roxas C, et al. Adherence to Inhaled Corticosteroids and Clinical Outcomes in Mepolizumab Therapy for Severe Asthma. *Eur Respir J*. 2020. doi:10.1183/13993003.02259-2019
38. Alahmadi FH, Simpson AJ, Gomez C, et al. Medication Adherence in Patients With Severe Asthma Prescribed Oral Corticosteroids in the U-BIOPRED Cohort. *Chest*. 2021;160:53–64. doi:10.1016/j.chest.2021.02.023
39. Tiotiu A. Applying personalized medicine to adult severe asthma. *Allergy Asthma Proc*. 2021;42:e8–16. doi:10.2500/aap.2021.42.200100
40. Taillé C, Devillier P, Dusser D, et al. Evaluating response to biologics in severe asthma: precision or guessimation? *Respir Med Res*. 2021;80:100813. doi:10.1016/j.resmer.2021.100813
41. Bossios A. Inflammatory T2 Biomarkers in Severe Asthma Patients: the First Step to Precision Medicine. *J Allergy Clin Immunol Pract*. 2021;9:2689–2690. doi:10.1016/j.jaip.2021.04.044

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