



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

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What is already known about this topic? In real life, biologic use is associated with significant improvement in asthma outcomes, but its effectiveness has not been established in patients with high oral corticosteroid exposure (HOCS) or compared with continuing with HOCS alone.

What does this article add to our knowledge? Continued HOCS and switch to biologics were both associated with improvement in severe asthma outcomes. However, patients with HOCS who initiated biologics experienced even greater improvements than those who continued with long-term or frequent rescue oral corticosteroids (OCSs).

How does this study impact current management guidelines? These findings may influence guidelines to recommend biologics, even in patients showing improvement on long-term or regular rescue OCSs, as a cost-effective strategy to improve outcomes while reducing OCS exposure.

Abbreviations used

BEC- blood eosinophil count
BMI- body mass index
ED- emergency department
GINA- Global Initiative for Asthma
GLM- generalized linear model
HCRU- health care resource utilization
HOCS- high oral corticosteroid exposure
ICS- inhaled corticosteroid
ISAR- International Severe Asthma Registry
LABA- long-acting β_2 -agonist
OCS- oral corticosteroid
RCT- randomized controlled trial
T2- type 2

BACKGROUND: Effectiveness of biologics has neither been established in patients with high oral corticosteroid exposure (HOCS) nor been compared with effectiveness of continuing with HOCS alone.

OBJECTIVE: To examine the effectiveness of initiating biologics in a large, real-world cohort of adult patients with severe asthma and HOCS.

METHODS: This was a propensity score–matched, prospective cohort study using data from the International Severe Asthma Registry. Between January 2015 and February 2021, patients with severe asthma and HOCS (long-term OCSs for ≥ 1 year or ≥ 4 courses of rescue OCSs within a 12-month period) were identified. Biologic initiators were identified and, using propensity scores, matched 1:1 with noninitiators. The impact of biologic initiation on asthma outcomes was assessed using generalized linear models.

RESULTS: We identified 996 matched pairs of patients. Both groups improved over the 12-month follow-up period, but improvement was greater for biologic initiators. Biologic initiation was associated with a 72.9% reduction in the average number of exacerbations per year versus noninitiators (0.64 vs 2.06; rate ratio, 0.27 [95% CI, 0.10-0.71]). Biologic initiators were 2.2 times more likely than noninitiators to take a daily long-term OCS dose of less than 5 mg (risk probability, 49.6% vs 22.5%; $P = .002$) and had a lower risk of asthma-related emergency department visits (relative risk, 0.35 [95% CI, 0.21-0.58]; rate ratio, 0.26 [0.14-0.48]) and hospitalizations (relative risk, 0.31 [95% CI, 0.18-0.52]; rate ratio, 0.25 [0.13-0.48]).

CONCLUSIONS: In a real-world setting, including patients with severe asthma and HOCS from 19 countries, and within an

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environment of clinical improvement, initiation of biologics was associated with further improvements across multiple asthma outcomes, including exacerbation rate, OCS exposure, and health care resource utilization. © 2023 The Authors. Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>). (J Allergy Clin Immunol Pract 2023;11:2732-47)

Key words: Biologics; Effectiveness; ISAR; Oral corticosteroids; Real life

INTRODUCTION

Severe asthma refers to asthma that is uncontrolled despite high-dose inhaled corticosteroids (ICSs)/long-acting β_2 -agonists (LABAs) or that requires high-dose ICSs/LABAs to remain controlled.¹ It is thought to affect up to 10% of the total asthma population² and is associated with significant morbidity, mortality, and socioeconomic burden.^{3,4} Recent global characterization analyses showed the high treatment burden associated with severe asthma (more than one-third of patients with severe asthma were on Global Initiative for Asthma [GINA] step 5 treatment, and more than half received intermittent oral corticosteroid [OCS] bursts⁵) and the predominance of the eosinophilic phenotype.⁶ Despite this high treatment burden, it has been reported that more than half of these patients had poorly controlled disease and experienced more than 1 exacerbation per year on average.⁵ As a consequence, health care costs in severe asthma are disproportionately high, with direct costs higher than

for type 2 (T2) diabetes, stroke, or chronic obstructive pulmonary disease⁷ and total costs accounting for more than 60% of total asthma expenditure.⁸

ICSs represent the cornerstone of asthma treatment.¹ However, there are 2 major limitations associated with their use: (1) local and systemic side effects, which are more common at higher doses, and (2) the persistence of exacerbations and poor control seen in some patients, predominantly among those with severe disease.^{9,10} For example, a survey in the United Kingdom found that 64% of patients with asthma taking ICSs reported 1 or more side effect.¹¹ GINA recommends short-course OCSs for those on medium-dose maintenance ICS/formoterol (step 4) whose initial presentation is with severely uncontrolled asthma or with an acute exacerbation.¹ Low-dose maintenance OCS is also an option that may be added at step 5 to high-dose ICS/LABA to control symptoms and minimize future exacerbation risk.¹ However, the cumulative burden of OCSs, from short-course and maintenance doses, is associated with adverse effects including obesity, diabetes, osteoporosis, cataract, hypertension, and adrenal suppression as well as psychological side effects such as depression and anxiety.¹² Indeed, even short-term OCS use is associated with sleep disturbance and increased risk of infection, fracture, and thromboembolism.¹³ Strategies to minimize need for OCSs are, therefore, a high priority.¹ According to OCS stewardship statements supported by the American College of Allergy, Asthma & Immunology and the American Lung Foundation (among others),¹⁴ “it is time to protect patients with asthma from potential over-exposure to OCS and to recognize OCS overuse for what it often is: a treatment plan failure.”¹⁴

Biologics (including anti-IgE, anti-IL-5/5R, anti-IL-4R α , and anti-thymic stromal lymphopoietin) that target key

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This study was conducted by the Observational and Pragmatic Research Institute Pte Ltd and was partially funded by OPC Global and AstraZeneca. No funding was received by the Observational and Pragmatic Research Institute for its contribution. Conflicts of interest: T. N. Tran is an employee of AstraZeneca (AZ), which is a cofounder of the International Severe Asthma Registry (ISAR). M. Sadatsafavi has received honoraria from AZ, Boehringer Ingelheim (BI), and GlaxoSmithKline (GSK) for purposes unrelated to the content of this article; and research funding from AZ and BI directly into his research account from AZ for unrelated projects. N. Ali was an employee of the Observational and Pragmatic Research Institute (OPRI) at the time this research was conducted. OPRI conducted this study in collaboration with Optimum Patient Care (OPC) and AZ. L. Bulathsinhala is an employee of OPRI, which conducted this study in collaboration with OPC Global and AZ. E. G. Gil was an employee of AZ at the time this research was conducted. J. M. FitzGerald reports grants from AZ, GSK, Sanofi Regeneron, and Novartis, paid directly to UBC; and received personal fees for lectures and attending advisory boards for AZ, GSK, Sanofi Regeneron, Novartis, and Teva Pharmaceuticals. M. Alacqua was an employee of AZ at the time this research was conducted. M. Al-Ahmad has received advisory board and speaker fees from AZ, Sanofi, Novartis, and GSK. A. Altraja has received lecture fees from AZ, BI, Berlin-Chemie Menarini, Chiesi, GSK, MSD, Norameda, Novartis, Sanofi, Zentiva, and Orion; sponsorships from AZ, BI, Berlin-Chemie Menarini, Chiesi, GSK, MSD, Norameda, Sanofi, and Novartis; and has been a member of advisory boards for AZ, BI, GSK, Novartis, Sanofi, and Teva Pharmaceuticals. R. Al-Lehebi has given lectures at meetings supported by AZ, BI, GSK, and Sanofi; and has received advisory board fees from GSK. M. Bhutani has received advisory board and speaker fees from AZ, GSK, Pfizer, Sanofi Genzyme, Covis Pharmaceuticals, Valeo, and Grifols; and has been an investigator on clinical trials sponsored by AZ, GSK, Sanofi Genzyme, and BI. L. Bjermer has received lecture or advisory board fees from ALK-Abelló, AZ, BI, Chiesi, GSK, Mundipharma, Novartis, Sanofi, Genzyme/Regeneron Pharmaceuticals, and Teva Pharmaceuticals. A.-S. Bjerrum

mediators of the T2 inflammatory cascade can be effective to achieve that aim. They are recommended for patients with severe asthma with exacerbations or poor symptom control on high-dose ICSs/LABAs, who have increased levels of T2 biomarkers (eg, high blood eosinophil count [BEC]) or need maintenance OCS.¹ Their efficacy and safety are well established within the randomized controlled trial (RCT) setting.¹⁵ A systematic review comparing the 5 current biologics to standard of care for severe eosinophilic asthma found that there is high certainty that all approved biologics reduce the rate of severe asthma exacerbations and that benralizumab, dupilumab, and mepolizumab reduce OCS use.¹⁵ However, these confirmatory efficacy studies are limited by restrictive eligibility criteria, relatively small patient populations, and varying study methodologies. As such, the generalizability of individual study results to the broader asthma population is limited.¹⁶

In real life, biologic use has been associated with a significant improvement in lung function and asthma control as well as a reduction in the number of asthma exacerbations and OCS use.¹⁷⁻²⁰ However, most real-life studies have been small, have used different definitions of severe asthma and asthma

exacerbations, and have included patients receiving widely varying OCS doses at baseline. Effectiveness of biologics has neither been established in patients with high OCS exposure (HOCS) nor been compared with the effectiveness of continuing with HOCS alone and not initiating biologic therapy.¹⁶

Our aim was to examine the effectiveness of initiating biologics in a large, real-world cohort of adult patients with severe asthma and HOCS.

METHODS

Study design and data source

This was a propensity score—matched, prospective cohort study using data from the International Severe Asthma Registry (ISAR); <https://isaregistry.org/>). Registry details have been described elsewhere.²¹ We included data from 19 countries (Argentina, Australia, Bulgaria, Canada, Colombia, Denmark, Greece, India, Ireland, Italy, Japan, Kuwait, Mexico, South Korea, Saudi Arabia, Spain, Taiwan, the United Arab Emirates, and the United Kingdom) that shared data with ISAR between January 2015 and February 2021. The study was designed, implemented, and reported in compliance with

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the European Network Centres for Pharmacoepidemiology and Pharmacovigilance Code of Conduct (European Medicine Agency 2014; European Union Electronic Register of Post-Authorisation Studies 33582) and with all applicable local and international laws and regulations. The ISAR database has ethical approval from the Anonymized Data Ethics Protocols and Transparency Committee (ADEPT0218).

Patients

Patients were required to be 18 years and older at enrollment and have severe asthma (ie, receiving treatment at GINA 2018 step 5 or with uncontrolled asthma at GINA step 4).²² See Table E1 in this article's Online Repository at www.jaci-inpractice.org for individual registry diagnostic and severe asthma criteria. Biologic prescription criteria variability between ISAR participating countries has been published elsewhere.²³ Patients were also required to have a history of HOCS defined as long-term use of OCSs for at least 1 year or 4 or more courses of rescue steroid bursts during the 12-month baseline period. The latter was agreed *a priori* and in line with previous publications.²⁴ Patients with HOCS were divided into the biologic-initiated group (who received biologics [anti-IgE, anti-IL-5/5R, and anti-IL-4R α]) and the biologic-not-initiated group (who were never administered a biologic). Effectiveness was assessed from the date of biologic initiation in the biologic-initiated group (which for some patients was before the first ISAR visit) and from the date of study entry for the biologic-not-initiated group. Various demographic and clinical variables of interest were retrieved on this date (eg, age, sex, ethnicity, and smoking status). An intention-to-treat approach was

applied, in which patients remained in the groups to which they were originally assigned, regardless of any potential changes in treatment (eg, stopped HOCS) over time. Previously, we found that only 10% of ISAR patients who initiated biologics stopped treatment.²⁵ Patients with a history of bronchial thermoplasty, with previous history of biologic use, or with inadequate background data on the date of initiation were excluded.

Propensity score matching

Propensity score matching was required because patients with severe asthma and HOCS who initiated biologics have different clinical characteristics than those who do not. These data have been published in detail elsewhere.²⁶ It was performed to obtain unbiased effectiveness estimates by comparing patients with severe asthma and HOCS who initiated biologics with those with similar clinical characteristics but who did not initiate biologics. Missing data were imputed using a robust multiple imputation approach before matching. Propensity score was derived using logistic regression, with initiation of biologics as the dependent variable. Covariates included age, sex, ethnicity, age at asthma onset, body mass index (BMI), BEC, smoking status, use of invasive ventilation, positive allergen test result, allergic rhinitis, chronic rhinosinusitis, eczema, nasal polyps, atopic condition, and geographical locations; all these covariates were measured at baseline, defined as within the past 12 months of biologic initiation or study entry for the biologic-initiated and the biologic-not-initiated groups, respectively. Of note, following expert recommendation, outcome history covariates were excluded in the matching to ensure objectivity of the study design.²⁷

the submitted work. D.-W. Perng (Steve) received sponsorship to attend or speak at international meetings; honoraria for lecturing or attending advisory boards; and research grants from AZ, BI, GSK, Novartis, Daiichi Sankyo, Shionogi, and Orient Pharma. M. Peters declares personal fees and nonfinancial support from AZ and GSK. P. E. Pfeffer has attended advisory boards for AZ and GSK; has given lectures at meetings supported by AZ and GSK; has taken part in clinical trials sponsored by AZ, GSK, Novartis, and Sanofi, for which his institution received remuneration; and has a current research grant funded by GSK. C. M. Porsbjerg has attended advisory boards for AZ, Novartis, Teva Pharmaceuticals, and Sanofi Genzyme; has given lectures at meetings supported by AZ, Novartis, Teva Pharmaceuticals, Sanofi Genzyme, and GSK; has taken part in clinical trials sponsored by AZ, Novartis, MSD, Sanofi Genzyme, GSK, and Novartis; and has received educational and research grants from AZ, Novartis, Teva Pharmaceuticals, GSK, ALK-Abelló, and Sanofi Genzyme. T. A. Popov declares relevant research support from Novartis and Chiesi. C. K. Rhee declares consultancy and lecture fees from AZ, BI, GSK, Mundipharma, MSD, Novartis, Sandoz, Sanofi, Takeda, and Teva Pharmaceuticals-Handok. S. Salvi declares research support and speaker fees from Cipla, Glenmark, and GSK. C. Taillé has received lecture or advisory board fees and grants to her institution from AZ, Sanofi, GSK, Chiesi, and Novartis, for unrelated projects. C. A. Torres-Duque has received fees as advisory board participant and/or speaker from AZ, BI, GSK, Novartis, and Sanofi Aventis; has taken part in clinical trials conducted by AZ, Novartis, and Sanofi Aventis; and has received unrestricted grants for investigator-initiated studies at Fundación Neumológica Colombiana from AZ, BI, GSK, Grifols, and Novartis. C. Ulrik has attended advisory boards for AZ, ALK-Abelló, GSK, BI, Novartis, Chiesi, Teva Pharmaceuticals, Covis Pharma, and Sanofi Genzyme; has given lectures at meetings supported by AZ, Sandoz, Mundipharma, Chiesi, BI, Orion Pharma, Novartis, Teva Pharmaceuticals, Sanofi Genzyme, and GSK; has taken part in clinical trials sponsored by AZ, Novartis, Merck, InsMed, ALK-Abelló, Sanofi Genzyme, GSK, BI, Regeneron Pharmaceuticals, Chiesi, and Novartis; and has received educational and research grants from AZ, Mundipharma, BI, Novartis, Teva Pharmaceuticals, GSK, and Sanofi Genzyme. S.-W. Ra has received lecture fees from AZ, BI, Chiesi, GSK, and Novartis. E. Wang has received honoraria from AZ, GSK, Wefight, and Clinical Care Options; and has been an investigator on clinical trials sponsored by AZ, GSK, Genentech, Sanofi, Novartis, and Teva Pharmaceuticals, for which her institution has received funding. M. E. Wechsler

reports grants and/or personal fees from Novartis, Sanofi, Regeneron Pharmaceuticals, Genentech, Sentien, Restorbio, Equillum, Genzyme, Cohero Health, Teva Pharmaceuticals, BI, AZ, Amgen, GSK, Cytoreason, Cerecor, Sound Biologic, Incyte, and Kinaset. D. B. Price reports advisory board membership with Amgen, AZ, BI, Chiesi, Circassia, Mylan, Mundipharma, Novartis, Regeneron Pharmaceuticals, Sanofi Genzyme, Teva Pharmaceuticals, and Thermo Fisher; consultancy agreements with Amgen, AZ, BI, Chiesi, GSK, Mylan, Mundipharma, Novartis, Pfizer, Teva Pharmaceuticals, and Theravance; grants and unrestricted funding for investigator-initiated studies (conducted through OPRI) from AZ, BI, Chiesi, Circassia, Mylan, Mundipharma, Novartis, Pfizer, Regeneron Pharmaceuticals, Respiratory Effectiveness Group, Sanofi Genzyme, Teva Pharmaceuticals, Theravance, and UK National Health Service; payment for lectures/speaking engagements from AZ, BI, Chiesi, Cipla, GSK, Kyorin, Mylan, Mundipharma, Novartis, Regeneron Pharmaceuticals, Sanofi Genzyme, and Teva Pharmaceuticals; payment for the development of educational materials from Mundipharma and Novartis; payment for travel/accommodation/meeting expenses from AZ, BI, Mundipharma, Mylan, Novartis, and Thermo Fisher; funding for patient enrollment or completion of research from Novartis; stock/stock options from AKL Research and Development Ltd, which produces phytopharmaceuticals; 74% ownership of the social enterprise OPC (Australia and United Kingdom) and 74% of OPRI (Singapore); 5% shareholding in Timestamp, which develops adherence monitoring technology; is a peer reviewer for grant committees of the Efficacy and Mechanism Evaluation Programme and Health Technology Assessment; and was an expert witness for GSK. The rest of the authors declare that they have no relevant conflicts of interest.

Received for publication September 20, 2022; revised May 29, 2023; accepted for publication May 30, 2023.

Available online June 8, 2023.

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<https://doi.org/10.1016/j.jaip.2023.05.044>

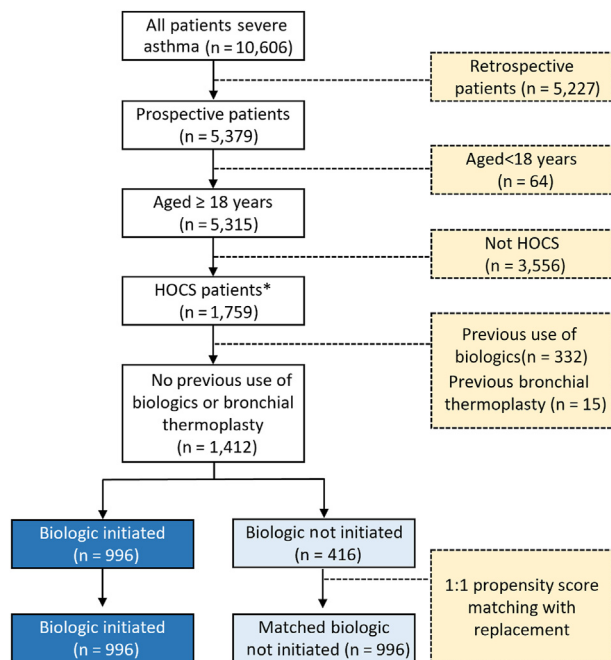


FIGURE 1. Subject disposition. *Long-term use of OCSs for at least 1 year or 4 or more courses of rescue steroid bursts during the 12-month baseline (preindex) period.

A 1:1 nearest neighbor matching with replacement and subsequent regression analyses was then performed, such that the nonbiologic patients could be matched to 1 or more biologic users (see the Online Repository at www.jaci-inpractice.org).

Outcome variables

The primary outcome was reduced rate of asthma exacerbations with initiation of a biologic therapy, compared with noninitiation. The secondary outcomes included improvement in asthma control, reduction in OCS dose, and reduced number of asthma-related emergency department (ED) visits and asthma-related hospital admissions. The exploratory outcome included reduced risk of OCS-related comorbidities. All outcomes were estimated during a 365-day follow-up period. Definitions and longitudinal measurements are provided in [Table E2](http://www.jaci-inpractice.org) in this article’s Online Repository at www.jaci-inpractice.org.

Statistical analyses

The statistical analysis plan was predefined, and analyses were performed using Stata version 17 (StataCorp, College Station, Tex). Continuous and categorical data were described as mean ± SD and n (%), respectively. Overall, we used generalized linear models (GLMs; with the choice of the distribution and link function depending on the nature of the dependent variable) with generalized estimating equations to obtain robust inference by accounting for clustering (matched pairs and time-series measurements of specific outcomes). All regression analyses were adjusted for the follow-up period (ie, follow-up days were included either as a covariate in the linear and logistic regressions or as an off-set variable in the Poisson and negative binomial regressions, for the specific type of outcomes). The impact of biologic initiation on outcomes was estimated as marginal effects during the first 365 days of follow-up.

Outcomes were not reported for all patients because our study included 9 longitudinal outcomes with different data types (eg, censored count and binary data, and time-series multinomial data), which were measured at irregularly repeated real-world clinic visits over time. To prevent uncertainty in assumption and potential bias associated with the use of complex imputation methods, we did not impute missing outcome data. The missing pattern of outcome data and the number of observations included in each outcome are provided in [Table E3](http://www.jaci-inpractice.org) in this article’s Online Repository at www.jaci-inpractice.org. Additional details are provided in the Online Repository.

Primary analysis

A GLM with negative binomial distribution was used to estimate change in rate of exacerbations due to biologic initiation. Using a special causal inference technique (ie, G-computation), covariate-adjusted effects of biologic initiation were estimated overall and according to age category, sex group, smoking status, BMI category, and eosinophilic phenotype (see [Figure E1](http://www.jaci-inpractice.org) in this article’s Online Repository at www.jaci-inpractice.org), with further adjustments for exacerbation history and variables whose distribution was still unbalanced (defined as standardized difference >0.25 after matching)²⁸ (ie, smoking status and ethnicity).

Secondary analyses

A GLM with multinomial distribution was used to estimate the change in OCS dose due to biologic initiation. OCS dose was categorized in 2 ways: (1) total cumulative OCS dose per day during follow-up, which included maintenance and burst dose, and (2) long-term cumulative OCS dose per day, which included maintenance dose only. Both total and long-term daily cumulative OCS dose reduction from baseline to follow-up were categorized as increased dose (<0% reduction), low dose reduction (0% to ≤50%), moderate dose reduction (>50% to ≤75%), and optimal dose reduction (>75%). An additional logistic regression was used to assess the likelihood of achieving low OCS use, with an OCS dose of less than 5 mg used to define both low total dose and low long-term dose. Independent variables were the same as the main OCS model. A GLM with multinomial distribution was used to assess change in asthma control. Health care resource utilization (HCRU) was assessed using a 2-part GLM separately for asthma-related ED visits and asthma-related hospitalizations. The first part was a probit model to estimate the probability of having any outcome event during follow-up, and the second part involved a negative binomial model to estimate the number of outcome events for those who had at least 1 event. An exploratory logistic regression was used to assess the incidence of any OCS-related comorbidities and any OCS-related chronic comorbidities (median follow-up period 721 days; interquartile range, 366-1182 days). All secondary analysis regressions were adjusted for unbalanced propensity score variables, exacerbation history, and the history of the corresponding secondary outcome.

Ethics Approval

This study was designed, implemented, and reported in compliance with the European Network Centres for Pharmacoepidemiology and Pharmacovigilance Code of Conduct (European Medicine Agency 2014; European Union Electronic Register of Post-Authorisation Studies 33582) and with all applicable local and international laws and regulations. Registration of the International Severe Asthma Registry (ISAR) database with the European Union Electronic Register of Post-Authorisation Studies was also

TABLE I. Postmatching baseline characteristics of propensity scoring variables

Characteristics	Biologic initiated (n = 996)	Biologic not initiated (n = 996)	SMD
Age (y), mean ± SD	51.7 ± 13.9	51.1 ± 14.6	-0.04
Sex, n (%)			
Male	387 (38.9)	296 (29.7)	0.19
Female	609 (61.1)	700 (70.3)	
Ethnicity, n (%)			
White	689 (69.2)	682 (68.5)	
Asian	62 (6.2)	65 (6.5)	
African	36 (3.6)	42 (4.2)	0.34*
Mixed	17 (1.7)	55 (5.5)	
Other	83 (8.3)	108 (10.8)	
Unknown	109 (10.9)	46 (4.6)	
Age of asthma onset (y), mean ± SD	28.4 ± 18.7	28.2 ± 18.8	-0.01
BMI (kg/m ²), mean ± SD	29.3 ± 6.8	28.5 ± 7.4	-0.11
BEC (n/mL), mean ± SD	479.8 ± 469.7	527.4 ± 471.3	0.10
Smoking status, n (%)			
Current smoker	25 (2.5)	70 (7.0)	
Ex-smoker	285 (28.6)	210 (21.1)	0.27*
Nonsmoker	686 (68.9)	716 (71.9)	
Invasive ventilation, n (%)	69 (6.9)	138 (13.9)	0.23
Positive allergen test result, n (%)	618 (62.0)	623 (62.6)	0.04
Allergic rhinitis, n (%)	313 (31.4)	302 (30.3)	0.08
Chronic rhinosinusitis, n (%)	246 (24.7)	167 (16.8)	0.20
Eczema, n (%)	98 (9.8)	61 (6.1)	0.14
Nasal polyps, n (%)	351 (35.2)	266 (26.7)	0.19
Atopic sensitization, n (%)	819 (82.2)	866 (86.9)	0.13
Country, n (%)			
Argentina	1 (0.1)	1 (0.1)	
Australia	43 (4.3)	43 (4.3)	
Bulgaria	4 (0.4)	3 (0.3)	
Canada	23 (2.3)	26 (2.6)	
Colombia	1 (0.1)	1 (0.1)	0.22
Denmark	170 (17.1)	124 (12.4)	
Greece	10 (1.0)	9 (0.9)	
India	0 (0.0)	0 (0.0)	
Ireland	0 (0.0)	0 (0.0)	
Italy	136 (13.7)	132 (13.3)	
Japan	6 (0.6)	8 (0.8)	
Kuwait	70 (7.0)	73 (7.3)	
Mexico	9 (0.9)	3 (0.3)	
Saudi Arabia	15 (1.5)	18 (1.8)	
South Korea	2 (0.2)	1 (0.1)	
Spain	7 (0.7)	7 (0.7)	
Taiwan	4 (0.4)	3 (0.3)	
United Arab Emirates	0 (0.0)	0 (0.0)	
United Kingdom	495 (49.7)	547 (54.9)	

SMD, Standardized mean difference.

*Following guideline recommendation, a standardized difference ranging 0.1 or 0.25 represents acceptable standardized biases. Covariates with a standardized difference of >0.25 were adjusted in the regression analyses.

undertaken (ENCEPP/DSPP/23720). ISAR has ethical approval from the Anonymized Data Ethics Protocols and Transparency Committee (ADEPT0218). Governance was provided by the Anonymized Data Ethics Protocols and Transparency Committee

(registration no. ADEPT0420). All data collection sites in the ISAR have obtained regulatory agreement in compliance with specific data transfer laws, country-specific legislations, and relevant ethical boards and organizations.

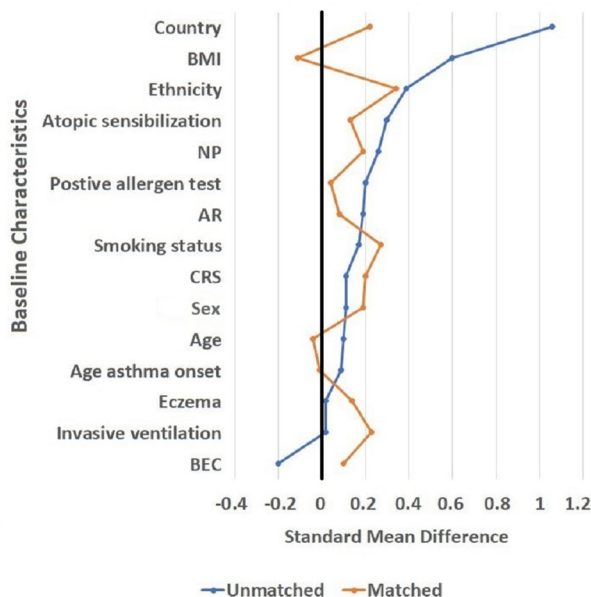


FIGURE 2. Comparison of pre- and post-propensity score matching baseline characteristics. The matched cohort included data on 996 patients who initiated biologics and 996 patients who did not. These patients were matched for baseline characteristics shown on the y-axis. Patients were not matched by baseline characteristics in the unmatched cohort, which comprised 996 patients who initiated biologics and 416 who did not. *AR*, Allergic rhinitis; *CRS*, chronic rhinosinusitis; *NP*, nasal polyp.

Data Availability

In line with ISAR governance restrictions, sharing individual deidentified participant data is subject to the consent of the ISAR Steering Committee members 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 (European Union Electronic Register of Post-Authorisation Studies 38128). 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.

RESULTS

Patients

Between January 2015 and February 2021, of the 10,606 adult patients with severe asthma from 19 ISAR participating countries, there were 5379 prospectively recruited patients, of whom 1412 had HOCS during the baseline period and met the inclusion criteria. The median follow-up period was 597 days, with an interquartile range of 360 to 964 days. Among these patients, 996 (70.5%) initiated biologics and 416 (29.5%) did not (Figure 1). All those who initiated a biologic were kept and matched with those who did not initiate a biologic (with replacement), yielding 996 patients per group (Figure 1). Of those who initiated a biologic, most ($n = 604$; 62.7%) were prescribed mepolizumab, followed by omalizumab ($n = 260$; 27.0%). Relatively small proportions of patients initiated

TABLE II. Postmatching baseline clinical characteristics

Characteristics	Biologic initiated (n = 996)	Biologic not initiated (n = 996)	SMD
No. of asthma exacerbations in the past year, mean \pm SD	5.1 \pm 4.1	5.0 \pm 3.8	-0.02
Long-term OCSs, n (%)	612 (61.4)	508 (51.0)	0.21
Total daily OCS dose (mg)			
Mean \pm SD	16.11 \pm 15.69	12.45 (7.31)	-0.299
Interquartile range	6.64-16.58	8.29-21.10	
Long-term daily OCS dose (mg)			
Mean \pm SD	12.72 \pm 8.92	9.99 \pm 6.21	-0.356
Interquartile range	5.00-12.50	5.00-20.00	
Asthma control, n (%) [*]			
Well controlled	51 (6.0)	35 (4.1)	0.12
Partially controlled	98 (11.6)	98 (11.6)	
Not controlled	628 (74.2)	713 (84.3)	
ED visits, mean \pm SD	1.7 \pm 4.3	1.8 \pm 3.7	0.02
Hospital admissions, mean \pm SD	0.9 \pm 2.0	0.9 \pm 1.6	0.00
ICS adherence, n (%)			
Adherent	774 (88.7)	603.5 (69.7)	0.50
Poor: clinical impression	12 (1.4)	74.8 (8.6)	
Poor: prescription records	87 (10.0)	187.5 (21.7)	

SMD, Standardized mean difference.

^{*}Assessed by GINA asthma control criteria,¹ Asthma Control Questionnaire,²⁹ or Asthma Control Test.³⁰

benralizumab ($n = 82$; 8.5%), reslizumab ($n = 12$; 1.2%), and dupilumab ($n = 6$; 0.6%).

Baseline characteristics: Propensity matching

After propensity score matching, biologic-initiated and biologic-not-initiated cohorts were well balanced for age, sex, ethnicity, age of asthma onset, BMI, BEC, smoking status, history of invasive ventilations, testing positive for allergen tests (either skin prick test to aeroallergens or serum specific IgE to aeroallergens), atopic sensitization (being recorded as atopic), the incidence of relevant comorbidities, and country (Table I; Figure 2).

The pre- and postmatching baseline characteristics are provided in Table E4 in this article's Online Repository at www.jaci-inpractice.org, and the propensity score distribution is displayed in Figure E2 in this article's Online Repository at www.jaci-inpractice.org. Of note, although eosinophilic gradient phenotype was not a propensity scoring variable, most matched patients from both the biologic-initiated and the biologic-not-initiated groups were in ISAR eosinophilic grade 3: most likely eosinophilic (89% and 75%, respectively) (Table E4). Patients were also well matched for asthma exacerbation rate, long-term and total OCS dose, asthma control, and HCRU (Table II). See Figure E3 in this article's Online Repository at www.jaci-inpractice.org for prevalence of OCS-related comorbidities per group.

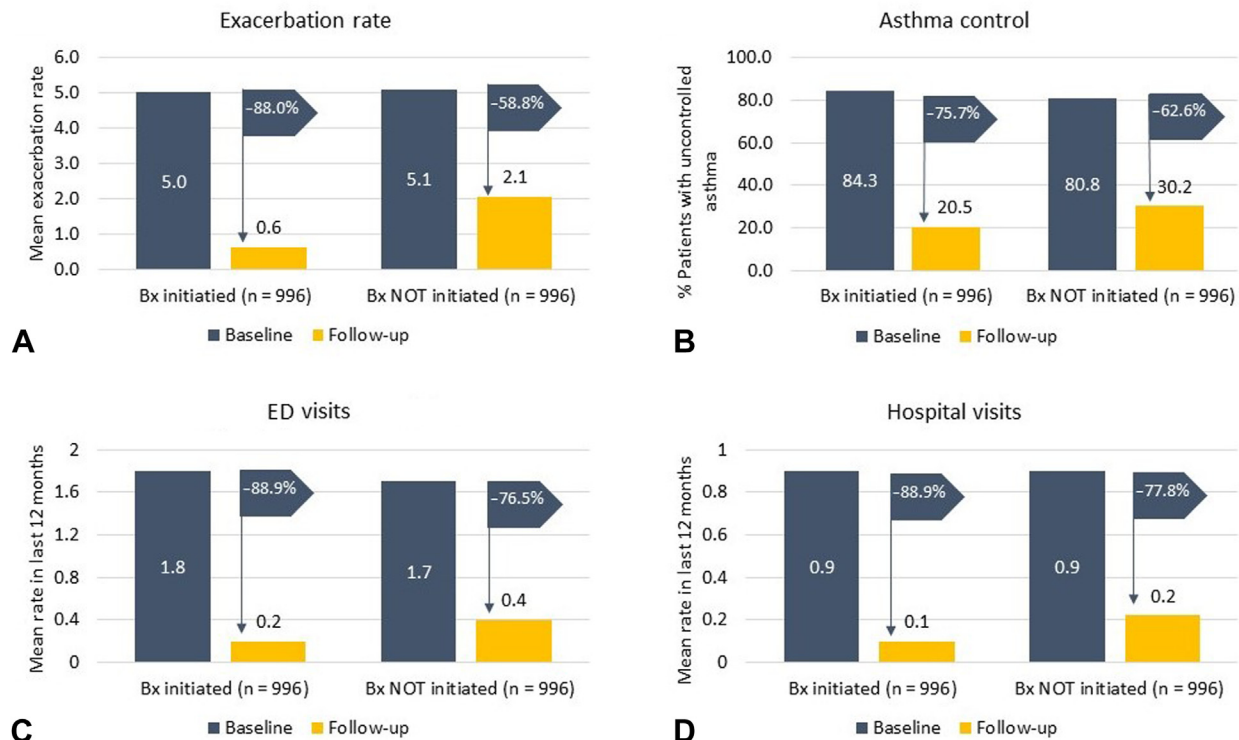


FIGURE 3. Change from baseline in (A) mean exacerbation rate/year,* (B) asthma control,† (C) asthma-related ED visit, and (D) asthma-related hospitalization in those who initiated and did not initiate biologic therapy. *Bx*, Biologic. *Defined as an event requiring rescue OCSs in the past year. †Asthma control was defined by GINA asthma control criteria,¹ Asthma Control Questionnaire,²⁹ or Asthma Control Test³⁰ in different settings.

Change from baseline in key efficacy variables

Improvements from baseline in asthma exacerbations and asthma control and reductions in HCRU (ie, asthma-related ED visits and hospitalizations) were noted both in those who initiated and in those who did not initiate biologic therapy. However, the improvements were greater in those who started biologics (Figure 3, A-D). For example, over a 12-month follow-up period, patients who initiated a biologic experienced an 88.0% reduction in exacerbation rate, compared with a 58.8% reduction in the biologic-not-initiated group (Figure 3, A). A similar differential between the biologic-initiated and the biologic-not-initiated groups was noted for asthma control (Figure 3, B), with superiority of the biologic-initiated group (vs the biologic-not-initiated group) also observed for the number of ED visits (Figure 3, C) and hospital admissions (Figure 3, D).

Exacerbation rate

In the regression analysis of propensity score–matched cohorts, biologic initiation was associated with an estimated average reduction of 1.43 exacerbations per year relative to the biologic-not-initiated group in the first year (0.64 vs 2.06; rate ratio, 0.27 [95% CI, 0.10-0.71]), corresponding to a 72.9% reduction (Figure 4). This pattern of estimated rate reduction remained consistent across age, sex, smoking status, BMI, and eosinophilic phenotypic categories.

OCS exposure

Patients who initiated a biologic were 2.48 times more likely to achieve a daily total OCS dose (ie, maintenance plus burst) of

less than 5 mg compared with the biologic-not-initiated group (estimated risk probability of 38.0% vs 15.3%; $P = .011$) and 2.20 times more likely to achieve a daily long-term OCS dose (ie, maintenance dose only) of less than 5 mg (risk probability, 49.6% vs 22.5%; $P = .002$). Compared with those who did not initiate a biologic, those who initiated a biologic were also 3.82 times (95% CI, 1.58-9.25) more likely to have a moderate (50% to $\leq 75\%$) total OCS reduction from baseline (risk probability, 16.2% vs 5.5%; $P = .001$) and tended to be 7.73 times (95% CI, 0.71-84.27) more likely to have an optimal ($>75\%$) total OCS reduction (risk probability, 13.4% vs 3.3%; $P = .063$) (Table III).

Asthma control and OCS-related comorbidities

No significant difference in the likelihood of having controlled asthma was observed within the first year (biologic-initiated vs biologic-not-initiated relative risk for staying uncontrolled was 0.66 [95% CI, 0.37-1.16]). Likewise, the 365-day risk of any new OCS-related comorbidity was very low in both groups, and the difference was uncertain given the wide CIs of relative risks (Table IV).

Health care resource utilization

Initiation of biologics was associated with a reduction in risk of asthma-related ED visits by 0.09, corresponding to a 65.0% reduction ($P = .003$) compared with the biologic-not-initiated group. Adjusted ED visit in the first year was 0.12 for those who initiated biologics compared with 0.33 for those who did not (rate ratio, 0.26 [95% CI, 0.14-0.48]) (Table V). Biologic

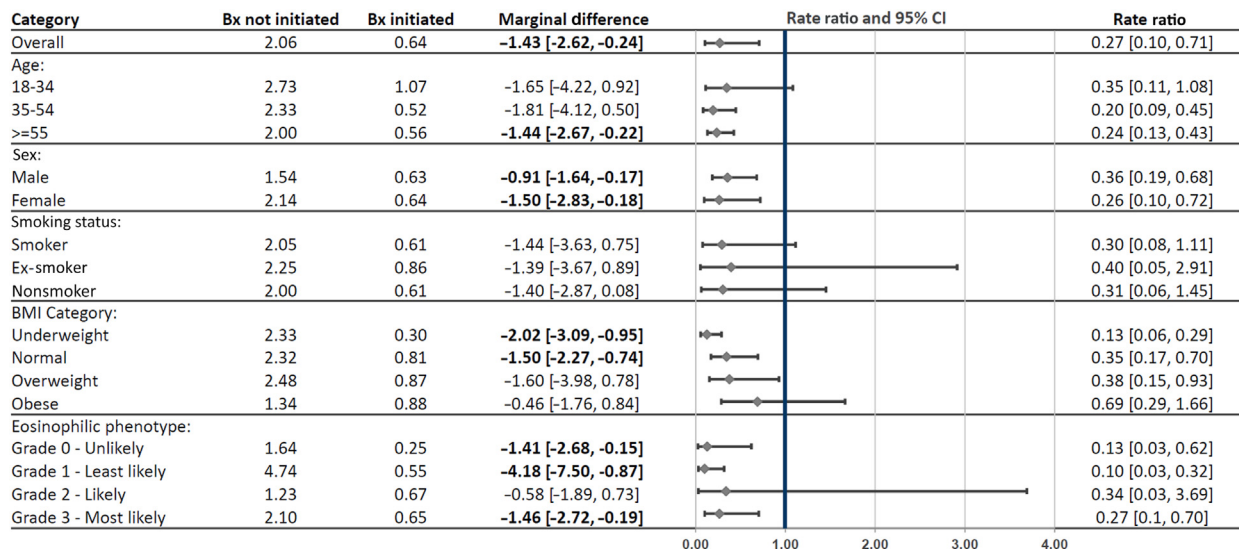


FIGURE 4. Effectiveness of biologic initiation vs noninitiation on mean exacerbation rate (in the next 365 days)* reduction in patients with severe asthma and high OCS exposure. Results are expressed as marginal rate difference (95% CI) and rate ratio (95% CI). *Bx*, Biologic. *Sample sizes vary because outcomes were not reported for all patients. The following are the number of per-patient observations used in the regression provided for each category for the biologic-not-initiated group and the biologic-initiated group, respectively: overall (n = 634/n = 801); age 18 to 34 years (n = 127/n = 111); age 35 to 54 years (n = 251/n = 345); age 55 years or more (n = 256/n = 345); male (n = 174/n = 316); female (n = 460/n = 485); smoker (n = 63/n = 18); ex-smoker (n = 128/n = 219); nonsmoker (n = 443/n = 219); underweight (n = 87/n = 11); normal weight (n = 137/n = 216); overweight (n = 175/n = 256); obese (n = 236/n = 318); grade 0 (n = 25/n = 3); grade 1 (n = 28/n = 24); grade 2 (n = 86/n = 51); and grade 3 (n = 496/n = 719). Exacerbation is defined as an event requiring rescue OCSs in the past year. Eosinophilic phenotype grades (0-3) are defined according to a previously published algorithm (Figure E1).⁶

therapy initiation was also associated with a 0.07 reduction in risk of experiencing any asthma-related hospitalization (69% reduction; *P* = .001), with the first-year frequency of asthma-

related hospitalizations of the biologic-initiated group being 25% of that of the biologic-not-initiated group (95% CI, 0.13-0.48; Table V).

TABLE III. Effectiveness of biologic initiation vs noninitiation on OCS reduction in 365 d

Outcome	Biologic not initiated	Biologic initiated	Marginal difference in % probability (95% CI)	Relative risk (95% CI)
Total OCSs				
% With†	N = 331*	N = 1071*		
Increased dose	27.6	16.0	-11.6 (-29.8 to 6.7)	0.51 (0.17 to 1.51)
Low reduction	63.6	54.4	-9.2 (-24.8 to 6.4)	0.87 (0.61 to 1.24)
Moderate reduction	5.5	16.2	10.7 (4.2 to 17.3)	3.82 (1.58 to 9.25)
Optimal reduction	3.3	13.4	10.0 (-0.6 to 20.7)	7.73 (0.71 to 84.27)
Long-term OCSs				
% With†	N = 311*	N = 1066*		
Increased dose	14.3	8.6	-5.7 (-18.0 to 6.5)	0.51 (0.12 to 2.17)
Low reduction	73.6	68.5	-5.1 (-22.5 to 12.3)	0.94 (0.69 to 1.28)
Moderate reduction	4.2	8.9	4.8 (-1.7 to 11.2)	2.55 (0.78 to 8.37)
Optimal reduction	7.9	14.0	6.1 (-7.7 to 19.9)	4.16 (0.21 to 82.18)

*No. of time-series observations; sample sizes vary because outcomes are not reported for all patients. The following are the numbers for each category for biologic-not-initiated and biologic-initiated groups, respectively: *Total OCSs*: total (n = 331/n = 1071); increased dose (n = 89/n = 118); low reduction (n = 203/n = 464); moderate reduction (n = 21/n = 173); and optimal reduction (n = 18/n = 316); *Long-term OCSs*: total (n = 311/n = 1066); increased dose (n = 48/n = 86); low reduction (n = 220/n = 597); moderate reduction (n = 12/n = 123); and optimal reduction (n = 31/n = 260).

†Increased dose (<0% reduction), low dose reduction (0% to ≤50%), moderate dose reduction (>50% to ≤75%), and optimal dose reduction (>75%).

TABLE IV. Effectiveness of biologic initiation vs noninitiation on asthma control* and new incidence of OCS-related comorbidities† in 365 d

	Biologic not initiated	Biologic initiated	Marginal difference in % probability (95% CI)	Relative risk (95% CI)
<i>Asthma control</i>				
% Patients	N = 177‡	N = 354‡		
Well controlled	49.5	51.1	1.6 (−22.0 to 25.2)	1.04 (0.58 to 1.84)
Partly controlled	20.3	28.5	8.1 (−16.1 to 32.3)	1.57 (0.46 to 5.38)
Uncontrolled	30.2	20.5	−9.7 (−22.7 to 3.2)	0.66 (0.37 to 1.16)
<i>Comorbidity incidence</i>				
% Patients with	N = 252‡	N = 380‡		
Any OCS-related comorbidity	0.18	2.31	2.13 (−1.81 to 6.07)	12.74 (1.12 to 144.82)
Any OCS-related chronic comorbidity	0.11	2.00	1.88 (−1.58 to 5.35)	26.02 (0.22 to 3025.63)

*Assessed by GINA asthma control criteria,¹ Asthma Control Questionnaire,²⁹ or Asthma Control Test.³⁰

†New OCS-related comorbidities include osteoporosis, heart failure, myocardial infarction, stroke, pulmonary embolism, glaucoma, cataract, renal failure, depression, anxiety, T2 diabetes, peptic ulcer, pneumonia, and obstructive sleep apnea. OCS-related chronic comorbidities include osteoporosis, heart failure, myocardial infarction, stroke, pulmonary embolism, glaucoma, cataract, renal failure, T2 diabetes, peptic ulcer, and obstructive sleep apnea.

‡No. of patients; sample sizes vary because outcomes are not reported for all patients. The following are the numbers for each category for biologic-not-initiated and biologic-initiated groups, respectively: *Asthma control*: total (n = 177/n = 354); well controlled (n = 83/n = 164); partly controlled (n = 50/n = 104); and uncontrolled (n = 44/n = 86); *Comorbidity incidence*: total (n = 9/n = 70); any OCS-related comorbidity (n = 6/n = 39); and any OCS-related chronic comorbidity (n = 3/n = 31).

DISCUSSION

Accurate estimation of biologic effectiveness in real life is important, because it may influence guideline recommendations for biologic use, as well as access, choice, and cost-effectiveness of prescribed biologics. In this global study, we assessed biologic effectiveness across a range of clinical outcomes in patients with severe asthma and HOCS to reflect the overuse and overreliance on OCS in real life,^{14,31} considering their potential to cause serious side effects and irreversible harm.^{12,13} We found that improvement in exacerbation rate, asthma control, and HCRU occurred in patients with severe asthma and HOCS irrespective of subsequent biologic initiation, highlighting the value of severe asthma services especially in terms of background therapy choice and adherence. However, those patients who initiated biologics showed the greatest improvements, exhibiting a 72.9% greater reduction in exacerbation rate and approximately one-third the risk and frequency of asthma-related ED visits and hospitalizations (ie, serious exacerbations) compared with patients who did not initiate a biologic treatment. These additional benefits are likely caused by direct effects of biologics themselves over and above those associated with tertiary care management in these

patients with evidence of eosinophilic asthma, a phenotype associated with more severe exacerbations and poorer asthma control.³² Initiation of biologic therapy may also have cost-saving potential considering that the mean direct cost of treating a hospitalization for a severe exacerbation has recently been estimated at €4997 per exacerbation.³³ This superiority of biologics was noted within an environment of improving asthma control in both groups as well as reduced OCS exposure in the biologic group. Patients who initiated biologics had a 2 times higher chance of achieving a daily long-term OCS dose of less than 5 mg and a 4 times higher chance of reducing their total OCS dose by more than 75% from baseline than patients who did not initiate a biologic.

Despite available care, recurrent asthma exacerbations are an issue in a proportion of patients with severe asthma.^{2,34} RCT data have found a biologic-associated reduction in exacerbation rate of 49% for benralizumab,³⁵ 47% for mepolizumab,³⁶ 26% for omalizumab,³⁷ 41% to 50% for reslizumab,³⁸ and 48% for dupilumab,³⁹ and a 58.8% reduction compared with biologic noninitiators and an 88.0% reduction relative to baseline observed in the present study (all biologics combined). This is

TABLE V. HCRU in 365 d

Outcome	Biologic not initiated	Biologic initiated	Marginal difference	Relative risk (for risk)/rate ratio (for rate)
	N = 502*	N = 661*		
Risk of ED visit	14% [9%, 20%]	6% [4%, 7%]	−9% [−14%, −3%]	0.35 [0.21, 0.58]
Rate of ED visit	0.33 [0.12, 0.55]	0.12 [0.05, 0.20]	−0.21 [−0.37, 0.05]	0.26 [0.14, 0.48]
	N = 514*	N = 667*		
Risk of hospitalization	12% [8%, 16%]	5% [4%, 7%]	−7% [−10%, −3%]	0.31 [0.18, 0.52]
Rate of hospitalization	0.23 [0.13, 0.33]	0.10 [0.06, 0.14]	−0.13 [−0.23, −0.04]	0.25 [0.13, 0.48]

Square brackets represent the 95% confidence interval of the effect size.

*N is the per-patient observations used in the regression analysis.

remarkably similar to the 81% reduction in exacerbation rate recently reported for benralizumab in a real-life cohort of patients with severe asthma in the United Kingdom, an effect that was independent of previous biologic use.⁴⁰ Improved effectiveness of biologics in the present study may be a consequence of a broader and more heterogeneous population, the size of the study, or differences in the extent of OCS exposure and associated baseline exacerbation rate in the populations studied. Biologic use has also previously been associated with exacerbation rate reduction outside the controlled settings of RCTs, but results have been variable (ranging from a 30% to a 69% reduction),^{19,41,42} likely because of differences in the background characteristics of the biologic users in real-world settings. Our findings and those of others, therefore, confirm the usefulness of biologics in reducing the considerable exacerbation burden experienced by patients with severe asthma, and their potential for cost-saving in terms of reduced HCRU. Indeed, in the present study, biologic use was associated with a marked reduction in the risk of asthma-related hospitalizations.

It has been estimated that up to 60% of patients with severe asthma are prescribed OCSs,⁴³ and although OCSs undoubtedly have a place in short bursts for the treatment of exacerbations, steroid-related adverse events are common.¹³ Several steroid-sparing strategies are now available to physicians including referral to specialist asthma centers, improving adherence to treatment, adding on therapies such as long-lasting muscarinic antagonists and macrolides, and treating with biologics.^{1,43} In our study, patients treated with biologics were 2.48 times more likely to have a moderate long-term OCS reduction and 2.20 times more likely to achieve a daily long-term OCS dose of less than 5 mg, in agreement with other real-life studies, albeit in a small number of patients.^{17,19,44} For example, the real world corticosteroid-sparing effect of mepolizumab in patients with severe asthma study found that mepolizumab reduced daily OCS dose by 50% after 21 to 24 weeks of treatment.¹⁹ The value of OCS reduction with biologic therapy is clear, but perhaps we can be even more aggressive and institute personalized OCS-tapering algorithms as advocated by the oral corticosteroid elimination via a personalized reduction algorithm in adults with severe asthma trial.⁴⁵ Real-world evidence is needed to bridge the gap between clinical trials and clinical practice and to examine the long-term impact of steroid reduction on new OCS-related adverse events.

We found no difference in asthma control between the biologic-initiated and the biologic-not-initiated groups; both groups showed marked improvement in asthma control from baseline (see Figure 2, B). This could be a consequence of referral to, and management in, a severe asthma service. Detection of a positive control signal was also challenging in the present study because control was assessed categorically, making it more difficult to show a small change, particularly in an environment of clinical improvement. Interestingly, the European Academy of Allergy and Clinical Immunology also concluded in its recent systematic review of biologics that although some biologics probably improve asthma control with moderate certainty of evidence, none of them showed an improvement above the

minimal important difference threshold of 0.5.¹⁵ Others have postulated that this may be because either asthma control does not indicate improvements caused by reduced eosinophilic airway inflammation or a dissociation exists between symptoms and exacerbations in patients with severe asthma.⁴⁶ We also did not see the expected reduction in new incidence of OCS-related comorbidities in the biologic-initiated group, but our study was not designed to do so, and the few observed incidences and wide CIs introduced a high level of uncertainty in these findings. However, patients in the biologic-initiated group were more likely to have an OCS dose reduction than patients in the biologic-not-initiated group. A longer follow-up time may be required to observe this effect. Others have also found a disconnect between OCS reduction and toxicity.⁴⁷

Study limitations

Limitations of this study include those common to all observational studies, such as recall bias, as well as the potential for an initiation bias due to differences in socioeconomic and geographical factors not accounted for in the matching. Results may have been influenced by missing data, the uneven distribution of patients on each biologic, which was a consequence of the date of data development and requirement for a 1-year follow-up period, and intercountry variability in biologic access criteria.²³ This latter issue has been mitigated in another ISAR study, which found that anti-IL-5/5R biologics were more effective than anti-IgE in patients eligible for, and with access to, both classes.⁴⁸ In addition, there may be some confounding by country (eg, the United Kingdom was overrepresented in the biologic-initiated group, which may have skewed findings); however, this was accounted for during propensity score matching. Strengths of our study are the inclusion of a large, multinational severe and heterogeneous asthma cohort, generalizable to the severe asthma population. Rigorous statistical analyses were also used, including use of weighted and adjusted regression models and marginal effect estimates, and the potential for bias minimized by use of propensity score matching and multiple imputation.

CONCLUSIONS

In a real-world setting, initiation of biologics is associated with reduced exacerbation rate, OCS exposure, and HCRU in patients with severe asthma and HOCS.

Acknowledgments

We acknowledge Dr Alex de Giorgio-Miller, of AstraZeneca, and Dr James Zangrilli, formerly of AstraZeneca, for their instrumental contributions to the study concept, and Joash Tan, of the Observational and Pragmatic Research Institute, for editorial and formatting assistance, which supported the development of this publication. We also thank the investigators and participating sites in ISAR for making this research possible. The following is a list of the ISAR participating sites:

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REFERENCES

- Global Initiative for Asthma. Global strategy for asthma management and prevention. Accessed June 26, 2023. <https://ginasthma.org/wp-content/uploads/2022/07/GINA-Main-Report-2022-FINAL-22-07-01-WMS.pdf>
- Chung KF. Defining phenotypes in asthma: a step towards personalized medicine. *Drugs* 2014;74:719-28.
- Gupta RP, Mukherjee M, Sheikh A, Strachan DP. Persistent variations in national asthma mortality, hospital admissions and prevalence by socioeconomic status and region in England. *Thorax* 2018;73:706-12.
- Kerkhof M, Tran TN, Soriano JB, Golam S, Gibson D, Hillyer EV, et al. Healthcare resource use and costs of severe, uncontrolled eosinophilic asthma in the UK general population. *Thorax* 2018;73:116-24.
- Wang E, Wechsler ME, Tran TN, Heaney LG, Jones RC, Menzies-Gow AN, et al. Characterization of severe asthma worldwide: data from the International Severe Asthma Registry (ISAR). *Chest* 2020;157:805-14.
- Heaney LG, Perez de Llano L, Al-Ahmad M, Backer V, Busby J, Canonica GW, et al. Eosinophilic and non-eosinophilic asthma: an expert consensus framework to characterize phenotypes in a global real-life severe asthma cohort. *Chest* 2021;160:814-30.
- O'Neill S, Sweeney J, Patterson CC, Menzies-Gow A, Niven R, Mansur AH, et al. The cost of treating severe refractory asthma in the UK: an economic analysis from the British Thoracic Society Difficult Asthma Registry. *Thorax* 2015;70:376-8.
- Sadatsafavi M, Lynd L, Marra C, Carleton B, Tan WC, Sullivan S, et al. Direct health care costs associated with asthma in British Columbia. *Can Respir J* 2010;17:74-80.
- Henderson I, Caiazzo E, McSharry C, Guzik TJ, Maffia P. Why do some asthma patients respond poorly to glucocorticoid therapy? *Pharmacol Res* 2020;160:105189.
- Al Efraij K, Johnson KM, Wiebe D, Sadatsafavi M, FitzGerald JM. A systematic review of the adverse events and economic impact associated with oral corticosteroids in asthma. *J Asthma* 2019;56:1334-46.
- Cooper V, Metcalf L, Versnel J, Upton J, Walker S, Horne R. Patient-reported side effects, concerns and adherence to corticosteroid treatment for asthma, and comparison with physician estimates of side-effect prevalence: a UK-wide, cross-sectional study. *NPJ Prim Care Respir Med* 2015;25:15026.
- Lefebvre P, Duh MS, Lefeuvre MH, Gozalo L, Desai U, Robitaille MN, et al. Acute and chronic systemic corticosteroid-related complications in patients with severe asthma. *J Allergy Clin Immunol* 2015;136:1488-95.
- Waljee AK, Rogers MAM, Lin P, Singal AG, Stein JD, Marks RM, et al. Short term use of oral corticosteroids and related harms among adults in the United States: population based cohort study. *BMJ* 2017;357:j1415.
- Allergy & Asthma Network. Oral corticosteroid stewardship statement. Accessed June 26, 2023. <https://allergyasthmanetwork.org/wp-content/uploads/2020/07/oral-corticosteroid-stewardship-statement.pdf>
- Agache I, Beltran J, Akdis C, Akdis M, Canelo-Aybar C, Canonica GW, 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;75:1023-42.
- Calzetta L, Aiello M, Frizzelli A, Bertorelli G, Rogliani P, Chetta A. Oral corticosteroids dependence and biologic drugs in severe asthma: myths or facts? A systematic review of real-world evidence. *Int J Mol Sci* 2021;22:7132.
- Pelaia C, Calabrese C, Barbuto S, Busceti MT, Preianò M, Gallelli L, et al. Omalizumab lowers asthma exacerbations, oral corticosteroid intake and blood eosinophils: results of a 5-year single-centre observational study. *Pulm Pharmacol Ther* 2019;54:25-30.
- Dupin C, Belhadi D, Guilleminault L, Gamez AS, Berger P, De Blay F, et al. Effectiveness and safety of dupilumab for the treatment of severe asthma in a real-life French multi-centre adult cohort. *Clin Exp Allergy* 2020;50:789-98.
- Harrison T, Canonica GW, Chupp G, Lee J, Schleich F, Welte T, et al. Real-world mepolizumab in the prospective severe asthma REALITI—a study: initial analysis. *Eur Respir J* 2020;56:2000151.
- Wechsler ME, Peters SP, Hill TD, Ariely R, DePietro MR, Driessen MT, et al. Clinical outcomes and health-care resource use associated with reslizumab treatment in adults with severe eosinophilic asthma in real-world practice. *Chest* 2021;159:1734-46.
- FitzGerald JM, Tran TN, Alacqua M, Altraja A, Backer V, Bjermer L, et al. International Severe Asthma Registry (ISAR): protocol for a global registry. *BMC Med Res Methodol* 2020;20:212.

22. Global Initiative for Asthma. Global strategy for asthma prevention and treatment, 2018 update. Accessed June 26, 2023. <https://ginasthma.org/wp-content/uploads/2018/04/wms-GINA-2018-report-V1.3-002.pdf>
23. Porsbjerg CM, Menzies-Gow AN, Tran TN, Murray RB, Unni B, Audrey Ang SL, et al. Global variability in administrative approval prescription criteria for biologic therapy in severe asthma. *J Allergy Clin Immunol Pract* 2022;10:1202-16.
24. Sweeney J, Patterson CC, Menzies-Gow A, Niven RM, Mansur AH, Bucknall C, 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;71:339-46.
25. Menzies-Gow AN, McBrien C, Unni B, Porsbjerg CM, Al-Ahmad M, Ambrose CS, 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.
26. Chen W, Sadatsafavi M, Tran TN, Murray RB, Wong CBN, Ali N, et al. Characteristics of patients in the International Severe Asthma Registry with high steroid exposure who did and did not initiate biologic therapy. *J Asthma Allergy* 2022;15:1491-510.
27. Rubin DB. The design versus the analysis of observational studies for causal effects: parallels with the design of randomized trials. *Stat Med* 2007;26:20-36.
28. Rubin DB. Using propensity scores to help design observational studies: application to the tobacco litigation. *Health Serv Outcomes Res Methodol* 2001;2:169-88.
29. Juniper EF, Bousquet J, Abetz L, Bateman ED. Identifying "well-controlled" and "not well-controlled" asthma using the Asthma Control Questionnaire. *Respir Med* 2006;100:616-21.
30. Nathan RA, Sorkness CA, Kosinski M, Schatz M, Li JT, Marcus P, et al. Development of the asthma control test: a survey for assessing asthma control. *J Allergy Clin Immunol* 2004;113:59-65.
31. Blakey J, Chung LP, McDonald VM, Ruane L, Gornall J, Barton C, et al. Oral corticosteroids stewardship for asthma in adults and adolescents: a position paper from the Thoracic Society of Australia and New Zealand. *Respirology* 2021;26:1112-30.
32. Price DB, Rigazio A, Campbell JD, Bleecker ER, Corrigan CJ, Thomas M, et al. Blood eosinophil count and prospective annual asthma disease burden: a UK cohort study. *Lancet Respir Med* 2015;3:849-58.
33. Quirce S, Melero C, Huerta A, Uría E, Cuesta M. Economic impact of severe asthma exacerbations in Spain: multicentre observational study. *J Asthma* 2021;58:207-12.
34. Lugogo N, Judson E, Haight E, Trudo F, Chipps BE, Trevor J, et al. Severe asthma exacerbation rates are increased among female, Black, Hispanic, and younger adult patients: results from the US CHRONICLE Study. *J Asthma* 2022;59:2495-508.
35. Harrison TW, Chanez P, Menzella F, Canonica GW, Louis R, Cosio BG, et al. Onset of effect and impact on health-related quality of life, exacerbation rate, lung function, and nasal polyposis symptoms for patients with severe eosinophilic asthma treated with benralizumab (ANDHI): a randomised, controlled, phase 3b trial. *Lancet Respir Med* 2021;9:260-74.
36. Ortega HG, Liu MC, Pavord ID, Brusselle GG, FitzGerald JM, Chetta A, et al. Mepolizumab treatment in patients with severe eosinophilic asthma. *N Engl J Med* 2014;371:1198-207.
37. Humbert M, Beasley R, Ayres J, Slavin R, Hébert J, Bousquet J, et al. Benefits of omalizumab as add-on therapy in patients with severe persistent asthma who are inadequately controlled despite best available therapy (GINA 2002 step 4 treatment): INNOVATE. *Allergy* 2005;60:309-16.
38. Castro M, Zangrilli J, Wechsler ME, Bateman ED, Brusselle GG, Bardin P, 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;3:355-66.
39. Castro M, Corren J, Pavord ID, Maspero J, Wenzel S, Rabe KF, et al. Dupilumab efficacy and safety in moderate-to-severe uncontrolled asthma. *N Engl J Med* 2018;378:2486-96.
40. Jackson DJ, Burhan H, Menzies-Gow A, Pfeffer P, Nanzer A, Garcia Gil E, et al. Benralizumab effectiveness in severe asthma is independent of previous biologic use. *J Allergy Clin Immunol Pract* 2022;10:1534-44.
41. Trevor J, Lugogo N, Carr W, Moore WC, Soong W, Panettieri RAJ, et al. Severe asthma exacerbations in the United States: incidence, characteristics, predictors, and effects of biologic treatments. *Ann Allergy Asthma Immunol* 2021;127:579-587.e1.
42. Kimura Y, Suzukawa M, Inoue N, Imai S, Akazawa M, Matsui H. Real-world benefits of biologics for asthma: exacerbation events and systemic corticosteroid use. *World Allergy Organ J* 2021;14:100600.
43. Chung LP, Upham JW, Bardin PG, Hew M. Rational oral corticosteroid use in adult severe asthma: a narrative review. *Respirology* 2020;25:161-72.
44. Bjerrum AS, Skjold T, Schmid JM. Oral corticosteroid sparing effects of anti-IL-5/anti-IL-5 receptor treatment after 2 years of treatment. *Respir Med* 2021;176:106260.
45. Menzies-Gow A, Gurnell M, Heaney LG, Corren J, Bel EH, Maspero J, et al. Oral corticosteroid elimination via a personalised reduction algorithm in adults with severe, eosinophilic asthma treated with benralizumab (PONENTE): a multicentre, open-label, single-arm study. *Lancet Respir Med* 2022;10:47-58.
46. Pavord ID, Korn S, Howarth P, Bleecker ER, Buhl R, Keene ON, et al. Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial. *Lancet* 2012;380:651-9.
47. McDowell PJ, Stone JH, Zhang Y, Honeyford K, Dunn L, Logan RJ, et al. Glucocorticoid toxicity reduction with mepolizumab using the Glucocorticoid Toxicity Index. *Eur Respir J* 2022;59:2100160.
48. Pfeffer P, Ali N, Murray R, Ulrik C, Tran TN, Maspero JF, et al. Comparative effectiveness of Anti-IL-5 and Anti-IgE biologic classes in severe asthma patients eligible for both. *Allergy* 2023;78:1934-48.