

Impact of Biologics Initiation on Oral Corticosteroid Use in the International Severe Asthma Registry and the Optimum Patient Care Research Database: A Pooled Analysis of Real-World Data



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What is already known about this topic? Oral corticosteroids (OCS) are commonly used in severe asthma (SA) management, and cumulative exposure leads to numerous adverse effects. Although biologics substantially reduce OCS intake in clinical trials, real-world evidence remains limited.

What does this article add to our knowledge? Based on robust real-world evidence, patients with SA who initiate biologics would experience earlier and substantially greater TOCS reduction, with more than twice the likelihood of reducing OCS daily dose by greater than 75%, or complete cessation, in the first year.

How does this study impact current management guidelines? Our study provides robust real-world evidence for addressing international consensus on OCS tapering, highlighting the need for rigorous biologic-facilitated, personalized tapering strategies in real-world settings, and potentially early biologic intervention with rigorous first-year monitoring.

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Abbreviations used

BEC- Blood eosinophil count
ED- Emergency department
GINA- Global Initiative for Asthma
GLM- Generalized linear model
ISAR- International Severe Asthma Registry
OCS- Oral corticosteroid
OPCRD- Optimum Patient Care Research Database
PSM- Propensity score matching/matching
SA- Severe asthma
SMD- Standardized mean difference
TOCS- Total oral corticosteroids

BACKGROUND: For severe asthma (SA) management, real-world evidence on the effects of biologic therapies in reducing the burden of oral corticosteroid (OCS) use is limited.

OBJECTIVE: To estimate the efficacy of biologic initiation on total OCS (TOCS) exposure in patients with SA from real-world specialist and primary care settings.

METHODS: From the International Severe Asthma Registry (ISAR, specialist care) and the Optimum Patient Care Research Database (OPCRD, primary care, United Kingdom), adult biologic initiators were identified and propensity score-matched with non-initiators (ISAR, 1:1; OPCRD, 1:2). The impact of biologic initiation on TOCS (including bursts for

exacerbations) daily dose in the first- and second-year follow-up period was estimated using multivariable generalized linear models.

RESULTS: Among 5,663 patients (ISAR 48%, OPCRD 52%), the odds ratios (ORs) of biologic initiators achieving TOCS cessation in the first and second years of follow-up were 2.38 (95% CI, 1.87-3.04) and 2.11 (95% CI, 1.65-2.70), whereas the ORs of low (0- to 5-mg) TOCS intake were 1.62 (95% CI, 1.40-1.86) and 1.40 (95% CI, 1.21-1.61), respectively. Compared with non-initiators, biologic initiators had a substantially higher chance of achieving greater than 75% reduction from baseline (OR [95% CI] = 2.35 [2.06-2.68] and 1.53 [1.35-1.73] in first and second years, respectively). These findings remained persistent and robust when analyses were repeated with one country setting removed at a time.

CONCLUSIONS: Biologic initiation in patients with SA led to substantial reduction in TOCS exposure, particularly in the first year. Future analyses will explore the impact on OCS-related adverse health events. © 2025 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 license (<http://creativecommons.org/licenses/by/4.0/>). (J Allergy Clin Immunol Pract 2025;13:2033-48)

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INTRODUCTION

Approximately 5% to 10% of patients with asthma experience severe asthma (SA),¹ yet it disproportionately contributes to asthma-related morbidity, mortality, and comorbidities, and accounts for nearly 60% of asthma-related health care expenditure.^{2,3} Over half of patients with SA experience frequent severe exacerbations, defined as asthma attacks requiring oral corticosteroid (OCS) (≥ 20 mg prednisolone or its equivalent for ≥ 3 days) and/or resulting in emergency department (ED) visits or hospitalization, by the American Thoracic Society/European Respiratory Society Task Force criteria.⁴ SA exacerbations lead to

lung function decline⁵ and reduced quality of life,⁶ hindering asthma remission and complicating SA management.^{7,8} Consequently, patients with SA often require OCS as either long-term daily treatment or short bursts to manage exacerbations.^{4,9} Over 50% of patients with SA receive repeated OCS courses to relieve exacerbations,¹⁰ whereas 65% to 75% of users of intermittent OCS transitioned to frequent prescriptions over 10 years.¹¹ Moreover, 10% to 15% of patients with SA are prescribed long-term daily OCS for maintenance.¹¹⁻¹³ Before the approval of biologic treatments for SA,^{14,15} up to 57% of patients with refractory SA in the United Kingdom¹⁶ and 24% in Belgium¹⁷

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relied on long-term OCS. To date, OCS remains widely used in regions with limited access to biologics owing to cost, infrastructure, and regulatory barriers.¹⁸ Moreover, 40% of patients with SA have comorbidities associated with type 2 inflammation, such as nasal polyps, contributing to OCS exposure.¹⁹

However, OCS exposure shows a strong, dose-dependent link to adverse health events including osteoporosis, diabetes, and

psychiatric disorders.²⁰⁻²² In fact, even low cumulative OCS doses (eg, four lifetime courses²³) increase risks of sepsis and thromboembolism.²⁴ As such, OCS burden contributes to higher morbidity, mortality, reduced quality of life, and higher health care costs for patients with asthma.^{20,25-31} In the Severe Asthma Network in Italy registry, OCS-related adverse events cost €242.7 million annually, doubling that of patients with

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non-SA and tripling that of the non-asthma control cohort.²⁸ Consequently, a 2021 expert consensus recommended tapering OCS in all patients with asthma, advocating personalizing tapering to optimize safety and efficacy.³²

Targeted biologic therapies have emerged over the past few decades to manage SA and reduce exacerbations.³³⁻³⁵ Since then, numerous landmark trials have consistently demonstrated their superior efficacy in reducing exacerbations and improving symptom control and lung function while minimizing OCS use.³⁶⁻⁴⁶ However, real-world evidence on the OCS-sparing effect of biologics is limited because many OCS-tapering studies either lacked a non-biologic comparator group or focused only

on maintenance OCS,⁴⁷ making it difficult to capture the true impact of biologics on OCS intake. Current real-world evidence also lacks generalizability owing to small sample sizes.⁴⁸⁻⁵¹ The largest to date involved 2,000 patients with SA with high OCS intake,³⁵ inconsistent OCS tapering protocols, and varying biologic use across health care systems.

To bridge this knowledge gap, our study aimed to estimate the real-world effectiveness of initiation of the major different biologic medications on changes in daily total OCS (TOCS) intake, including both long-term and burst doses, via a pooled analysis of propensity score-matched (PSM) cohorts of patients with SA.

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METHODS

Data sources

We pooled individual-level data from two real-world databases for this study. The International Severe Asthma Registry (ISAR)⁵² included over 20,000 patients with SA recruited from asthma specialist clinics across 29 countries as of 2024, with clinical and health care use data collected both prospectively and retrospectively. The Optimum Patient Care Research Database (OPCRD)⁵³ was composed of electronic health records of over 27 million patients from more than 1,000 general practices across the United Kingdom. This study included only a subset of practices with a formal recording of specialist diagnoses and biologic prescribing, excluding those with a lower than minimum expected proportion of biologic prescriptions in the United Kingdom to ensure reliable biologic prescription records. By combining these two databases, the pooled analysis provided a unique opportunity to evaluate OCS intake in patients with SA across both primary and secondary care settings, while assessing the real-world effects of biologic treatment on OCS weaning.

Study design

This was a pooled analysis of PSM cohorts from ISAR and OPCRD, which compared changes in TOCS intake over a 2-year follow-up relative to a 12-month pre-index period between patients with SA who initiated biologics and those who did not (see Figure E1 in this article's Online Repository at www.jaci-inpractice.org). Non-biologic patients were those who used no biologics during the entire study period. Treatment decisions and choice of biologics were determined by treating physicians at each participating center, following country-specific regulatory guidelines. An intention-to-treat design was applied for biologic initiators to ensure pragmatic estimates that account for real-world practices, including non-adherence, switches, and discontinuation. The index date was defined as the date of biologic initiation, whereas for non-initiators, it was the date of study enrollment in the ISAR cohort, and for the OPCRD cohort, a random primary care visit date between 2018 and 2019. To ensure a sufficient period of observation for meaningful TOCS changes, all eligible patients were required to have 12 months or more of pre-index data and 300 days or more of follow-up data on TOCS intake. Follow-up data were censored at death ($n = 0$), withdrawal, loss to follow up, or 730 days from the index date, whichever came first.

Sample

Patients aged 18 years or greater with SA were included (see patient selection flowcharts in Figures E2 and E3 in this article's Online Repository at www.jaci-inpractice.org). In the ISAR cohort, SA was defined according to the 2018 Global Initiative for Asthma (GINA) criteria⁵⁴ as either receiving GINA Step 5 treatment or having uncontrolled disease while receiving Step 4 treatment (see country-specific definitions in Table E1 in this article's Online Repository at www.jaci-inpractice.org). In OPCRD, SA was defined as either receiving a biologic (ie, GINA Step 5 treatment) or having uncontrolled disease while receiving GINA Step 4 treatment (ie, having two or more exacerbations in the 12-month pre-index period and four or more lifetime TOCS bursts). Patients with missing index dates were excluded from the ISAR cohort ($n = 276$; <2%). To minimize confounding bias, patients were excluded if they had ever received bronchial thermoplasty or had comorbidities requiring regular OCS therapy (see Table E2 in this article's Online Repository at www.jaci-inpractice.org).

Matching

We applied PSM to balance treatment-related covariates between the exposed (eg, biologic initiators) and comparison groups to reduce bias in estimating treatment effects.⁵⁵ Aligning with randomized controlled trial (RCT)-based pooled analyses,⁵⁶⁻⁵⁸ we first performed PSM separately within the ISAR and OPCRD cohorts, followed by a pooled analysis of all matched pairs. Nearest-neighbor matching with replacement⁵⁹ was applied, which paired biologic initiators and non-initiators by closest propensity score. Matching ratios of 1:1 for the ISAR cohort and 1:2 for the OPCRD cohort were selected. The latter scheme was to improve matching efficiency in OPCRD given fewer biologic initiators and the large population of non-initiators.⁶⁰

The PSM used propensity (logit) scores to initiate biologics (caliper ≤ 0.1) based on the following covariates, all measured during the 12-month pre-index period: age, sex, body mass index, common risk factors for biologic initiation in ISAR⁶¹ (ie, levels of asthma control, blood eosinophil count [BEC], FEV₁ % predicted, FEV₁/FVC, number of exacerbations that required rescue OCS, and presence of nasal polyps), add-on therapies including leukotriene receptor antagonist and long-acting muscarinic antagonist, as well as long-term OCS use. In the OPCRD cohort, because the SA definition already aligned exacerbation frequency between initiators and non-initiators, we used asthma-related ED visits or acute hospitalization. Additionally, use of antibiotics was included to identify exacerbation history (see Table E3 in this article's Online Repository at www.jaci-inpractice.org). Following usual practice,⁶²⁻⁶⁴ we imputed missing values (inclusive of outliers and abnormal values) for covariates with less than 50% missingness using a robust, nonparametric random forest algorithm.⁶⁵

Outcome measures

The primary outcome was TOCS daily dose, including both long-term and burst doses, standardized to prednisolone-equivalent dose. Baseline dose (mg/day) was calculated by dividing the cumulative TOCS dose during the 12-month pre-index period by 365 days, which were specifically recorded in ISAR and naturally collected through patient enrollment in OPCRD. Follow-up dose (mg/day) was calculated for the first and second year after the index date, which divided cumulative TOCS dose during each follow-up year by the total number of days in that year.

Next, we derived five respective study end points for the first and second years of follow-up: (1) low TOCS daily dose, defined as 5 mg/day, including zero dose; (2) zero TOCS use; (3) any reduction (greater than zero) in TOCS daily dose compared with baseline; (4) optimal reduction (>75% reduction in TOCS daily dose compared with baseline, defined in accordance to previous ISAR publications³⁵); and (5) absolute change in TOCS daily dose compared with baseline (see Table E4 in this article's Online Repository at www.jaci-inpractice.org for additional details).

Statistical analysis

All analyses were conducted using R software (version 4.2.3, R Foundation for Statistical Computing, Vienna, Austria) and Stata software (version 17.1, College Station, Tex). Descriptive statistics for baseline patient characteristics and average TOCS daily dose over time were provided. To evaluate cohort balance (ie, systematic differences in the distribution of covariates), was calculated the absolute value of standardized mean difference (SMD) (see Figure E4 in this article's Online Repository at www.jaci-inpractice.org), with 0.1 or less indicating balance and 0.1 to 0.25 representing acceptable bias per guidelines.⁶⁶

For regression analysis, we used generalized linear models (GLMs) with generalized estimation equations to account for clustered time-series data in matched pairs. The regression model accounted for frequency weights, adjusting for potential unequal representation owing to matching with replacement in both cohorts and 1:2 matching in OPCR. Logistic regression within the GLM framework was applied to four binary end points: any reduction, optimal reduction, low, and zero TOCS daily dose, whereas a GLM with a Gaussian distribution modeled absolute changes in TOCS dose. The exposure variable was biologic initiation, and unbalanced covariates ($SMD > 0.1$), including BEC, exacerbation history, baseline TOCS daily dose, and their interactions with biologic initiation, were further adjusted.⁶⁷ Additionally, adjustments were made for follow-up years (first or second), interactions with biologic initiation, follow-up days, the index calendar year, the COVID-19 follow-up period (ie, after 2020), and ISAR/OPCR membership to account for unmeasured systematic differences between cohorts. Treatment effects were estimated as covariate-adjusted marginal differences for continuous end points and odds ratios (ORs) for binary end points at 365 and 730 days, comparing between biologic initiators versus non-initiators.

Sensitivity analysis

Because clinical evidence suggested that OCS reduction associated with anti-IgE is less pronounced compared with other types of biologics,⁶⁸ to reduce potential heterogeneity, we conducted a sensitivity analysis by excluding patients who initiated anti-IgE therapy. Likewise, in this analysis of international data, ensuring study findings were robust and not overly influenced by data from any single country was crucial. Following the principles of jackknife sensitivity analysis,⁶⁹ we iteratively excluded each country setting, refitted regressions on the remaining data, and pooled the five study end points at 365 and 730 days of follow-up using random-effects meta-analyses.

RESULTS

Patient characteristics

After excluding patients with missing index dates (ISAR: $n = 276$, $<2\%$; OPCR: $n = 0$), the final cohort included 3,323 matched pairs drawn from 5,663 patients with SA. A total of 1,356 biologic initiators were matched to 1,356 non-initiators from ISAR, and 984 biologic initiators were matched to 1,967 non-initiators from OPCR (see [Figures E2 and E3](#) in this article's Online Repository at www.jaci-inpractice.org). Most biologic initiators received anti-IL-5/5R α treatment (69% in ISAR and 45% in OPCR), followed by anti-IgE treatment (23% in ISAR and 26% in OPCR), anti-IL-4R α /13 treatment (8% in ISAR and 28% in OPCR), and anti-thymic stromal lymphopoietin treatment (2% in OPCR) (see [Figure E5](#) in this article's Online Repository at www.jaci-inpractice.org).

[Figure E4](#) presents the pre- and post-PSM SMD of covariates in ISAR and OPCR. The PSM successfully addressed systematic differences in most key factors influencing biologic prescription in both cohorts. However, some residual differences remained. Post-PSM, ISAR, and OPCR patients were comparable in the distributions of age, sex, body mass index, uncontrolled asthma, baseline exacerbations, lung function, long-term OCS use in general, and TOCS use in biologic initiators. Notably, biologic initiators had similar mean ($\pm$ SD) frequency of exacerbations in the past 12 months as non-initiators in ISAR, whereas the frequency was slightly higher in OPCR (ISAR: 2.9

± 2.8 vs 2.7 ± 2.9 , $SMD = -0.04$; OPCR: 3.1 ± 2.6 vs 2.8 ± 2.3 , $SMD = -0.11$) ([Table 1](#)). In ISAR, non-initiators were more likely to use long-term OCS (48.2% vs 40.9%; $SMD = 0.15$) and had lower baseline BEC (510.6 vs 586.3/ μ L; $SMD = -0.16$). These covariates were adjusted in the regression analyses. In OPCR, all other variables were balanced ($SMDs < 0.10$). Details on pre- and post-PSM comparisons are provided in [Tables E5 and E6](#) (in this article's Online Repository at www.jaci-inpractice.org).

Crude 3-year trends of TOCS intake

In the matched sample, both in ISAR and OPCR, biologic initiators had higher baseline TOCS daily doses compared with non-initiators (mean [SD]: ISAR, 6.5 [7.0] mg/day vs 5.9 [6.9] mg/day, $SMD = -0.09$; OPCR, 6.0 [7.0] mg/day vs 4.6 [5.1] mg/day, $SMD = -0.23$), which was adjusted in regressions ([Figure 1](#)). Over 2 years, substantial reductions in TOCS daily dose were observed among patients with SA in both initiator and non-initiator cohorts (ISAR, 3.3 [7.2] mg/day vs 3.7 [6.3] mg/day; relative reductions, 49.2% vs 37.3%, $SMD = 0.07$; OPCR, 4.0 [6.8] mg/day vs 3.1 [6.3] mg/day, relative reductions, 33.3% vs 25.9%, $SMD = -0.16$) ([Table 1](#)). [Figures E6 and E7](#) show (in this article's Online Repository at www.jaci-inpractice.org) show the relationship between baseline TOCS dose and absolute reductions in ISAR and OPCR, respectively. Whereas higher baseline dose correlated with greater reductions, initiators generally experienced greater reductions at similar baseline doses, both before and after PSM.

Adjusted effects of biologic initiation on achieving low TOCS intake

In the pooled analysis, biologic initiators were more likely to achieve low or zero OCS compared with non-initiators during the first and second years of follow-up. Biologic initiation compared with non-use was associated with a 1.62 times (95% CI, 1.40-1.86; 70% vs 63%) and 1.40 times (95% CI, 1.21-1.61; 73% vs 71%) higher chance of achieving a low TOCS daily dose (≤ 5 mg/day) in the first and second years, respectively ([Figure 2, A](#)). In particular, biologic initiation increased the chance of achieving zero TOCS use, with ORs of 2.38 (95% CI, 1.87-3.04, 28% vs 19%) in the first year and 2.11 (95% CI, 1.65-2.70, 33% vs 25%) in the second year ([Figure 2, A](#)). Excluding Anti-IgE initiators led to similar ORs of achieving low and zero TOCS (P s for differences in low-dose OR: .859 and .841 in the first and second years, respectively; P s for differences in zero-dose OR: .981 and .959 in the first and second years, respectively) ([Figure 2, B](#)).

Adjusted effects of biologic initiation on reduction of TOCS intake

Over 2 years, nearly 80% of both biologic initiators and non-initiators experienced reductions in TOCS intake. Biologic initiation relative to non-initiation was associated with a greater reduction by the first year, estimated at an OR of 1.13 (95% CI, 1.09-1.19) ([Figure 3, A](#)). Regarding the absolute scale of change, biologic initiation, compared with non-initiation, was associated with a greater and continuous reduction in TOCS daily dose ([Figure 4, A](#)) (respectively first year reductions, -2.44 vs -1.40 mg/day, excess reduction = -1.04 mg/day [95% CI, -1.35 to -0.74 mg/day]; second year reductions, -3.12 vs -2.64 mg/day, excess reduction = -0.48 mg/day [95% CI, -0.87 to

TABLE I. Post-matching patient characteristics* for ISAR and OPCRD cohorts

Demographics and disease characteristics	ISAR cohort			OPCRD cohort		
	Biologic not initiated (n = 1,356)	Biologic initiated (n = 1,356)	Standardized mean difference	Biologic not initiated (n = 1,967)	Biologic initiated (n = 984)	Standardized mean difference
Age, y (mean [SD])	54.1 (15.7)	53.4 (13.8)	0.05	49.4 (16.8)	50.2 (15.4)	−0.05
Sex, n (%)			0.04			0.02
Male	533 (39.3%)	561 (41.4%)		767 (39.0%)	392 (39.8%)	
Female	823 (60.7%)	795 (58.6%)		1,200 (61.0%)	592 (60.2%)	
Body mass index, kg/m ² (mean [SD])	28.8 (6.3)	28.4 (5.9)	0.08	29.8 (7.9)	29.9 (8.2)	−0.01
Symptom control in past 4 wk, n (%)			0.08			0.06
Well controlled	148 (10.9%)	183 (13.5%)		96 (4.9%)	36 (3.7%)	
Partially controlled	220 (16.2%)	225 (16.6%)		683 (34.7%)	343 (34.9%)	
Uncontrolled	989 (72.9%)	948 (69.9%)		1,188 (60.4%)	605 (61.5%)	
Blood eosinophil count (highest), mL (mean [SD])	510.6 (429.1)	586.3 (494.8)	−0.16	838.8 (556.3)	825.7 (518.2)	−0.02
FEV ₁ % predicted (mean [SD])	73.2 (23.5)	73.3 (22.8)	0.00	74.5 (23.7)	74.7 (22.8)	−0.01
FEV ₁ /FVC ratio (mean [SD])	0.7 (0.1)	0.7 (0.1)	0.04	0.7 (0.2)	0.7 (0.2)	0.04
Nasal polyps, n (%)	508 (37.5%)	551 (40.6%)	0.06	380 (19.3%)	204 (20.7%)	0.04
Use of leukotriene receptor antagonists, n (%)	354 (26.1%)	332 (24.5%)	0.04	53 (2.7%)	24 (2.4%)	0.02
Use of long-acting muscarinic antagonists, n (%)	338 (24.9%)	287 (21.2%)	0.09	867 (44.1%)	464 (47.2%)	0.06
Use of long-term OCS, n (%)	654 (48.2%)	555 (40.9%)	0.15	437 (44.2%)	438 (44.5%)	0.01
Use of antibiotics, n (%)	—	—	—	1,400 (71.2%)	697 (70.8%)	0.01
Exacerbations in past 12 mo (mean [SD])	2.7 (2.9)	2.9 (2.8)	−0.04	2.8 (2.3)	3.1 (2.6)	−0.11
Asthma-related emergency department visits or hospitalizations in past 12 mo (mean [SD])	0.7 (1.7)	0.6 (1.4)	0.09	0.2 (0.5)	0.2 (0.5)	0.01
Pre-index total daily OCS use (mean [SD]), mg	5.9 (6.9)	6.5 (7.0)	−0.09	4.6 (5.1)	6.0 (7.0)	−0.23
First year total daily OCS use, mg (mean [SD])	5.2 (7.5)	4.7 (8.0)	0.07	3.5 (4.9)	4.6 (7.0)	−0.18
Second year total daily OCS use, mg (mean [SD])	3.7 (6.3)	3.3 (7.2)	0.07	3.1 (6.3)	4.0 (6.8)	−0.16

ISAR, International Severe Asthma Registry; OCS, oral corticosteroids; OPCR, Optimum Patient Care Research Database.

*We performed propensity score matching within the ISAR and OPCR cohorts using baseline long-term oral corticosteroid use (yes/no) and other patient characteristics. The values for pre-index total daily OCS use, first year total daily OCS use, and second year total daily OCS use are presented as unadjusted data.

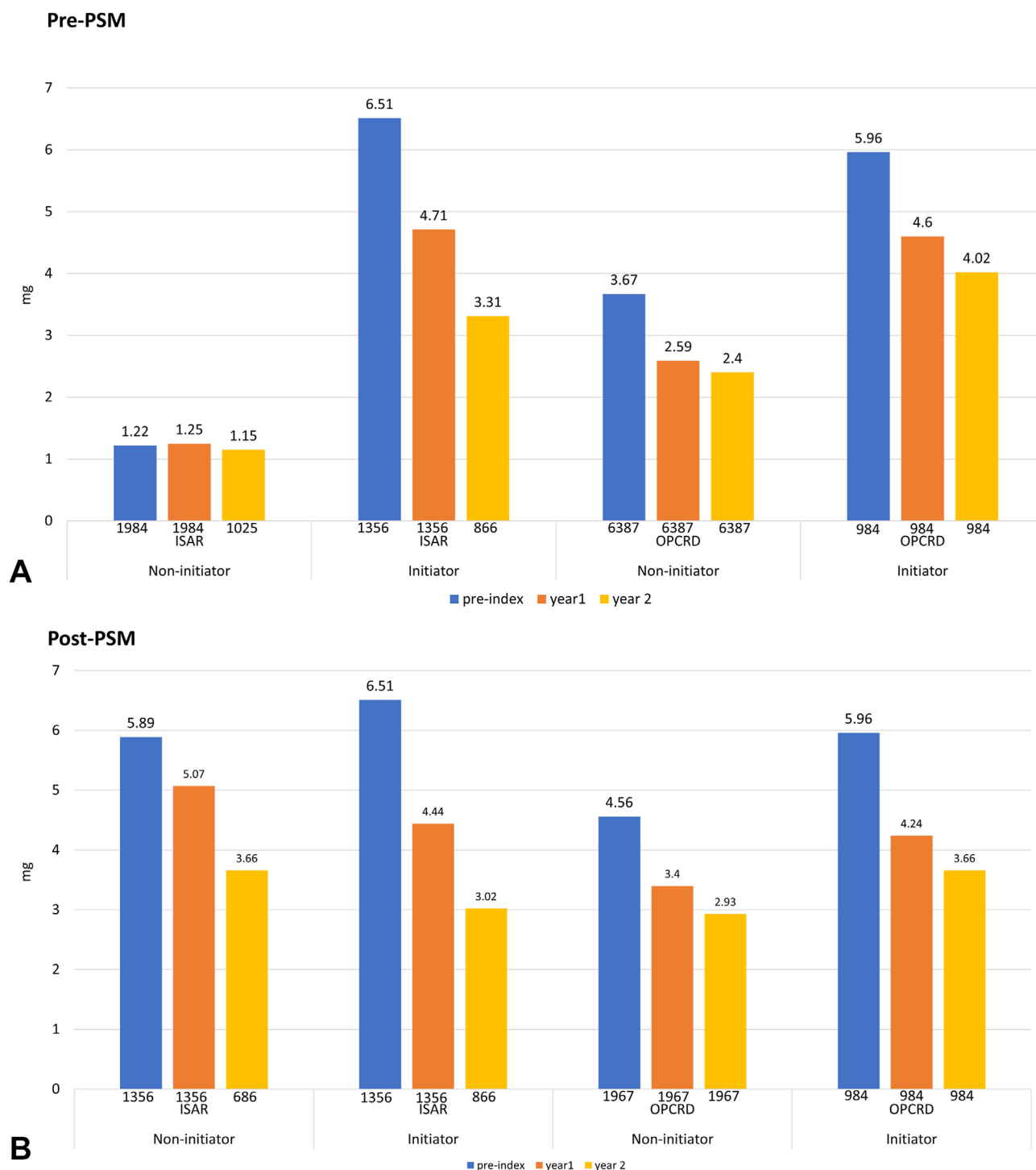


FIGURE 1. Distributions of mean oral corticosteroid daily dose over time for patients with baseline and at least 1 year of follow-up before and after propensity score matching (PSM). *ISAR*, International Severe Asthma Registry; *OPCRD*, Optimum Patient Care Research Database.

−0.08 mg/day]). Analyses excluding anti-IgE initiators showed similar results (*P*s for differences in excess reduction: .731 and .494 in the first and second years, respectively) (Figure 4, B).

Notably, biologic initiators had a significantly higher chance of achieving optimal TOCS reduction (>75% reduction, with an OR of 2.35 [95% CI, 2.06-2.68, 37% vs 21%] the first year

and 1.53 [95% CI, 1.35-1.73, 46% vs 37%] in the second year, compared with non-initiators (Figure 3, A). The corresponding ORs appeared similar (*P*s in comparison: .702 in year 1 and .673 in year 2), yet slightly increased when anti-IgE initiators were excluded (year 1: 2.44 [95% CI, 2.12-2.81], and year 2: 1.59 [95% CI, 1.40-1.81]) (Figure 3, B).

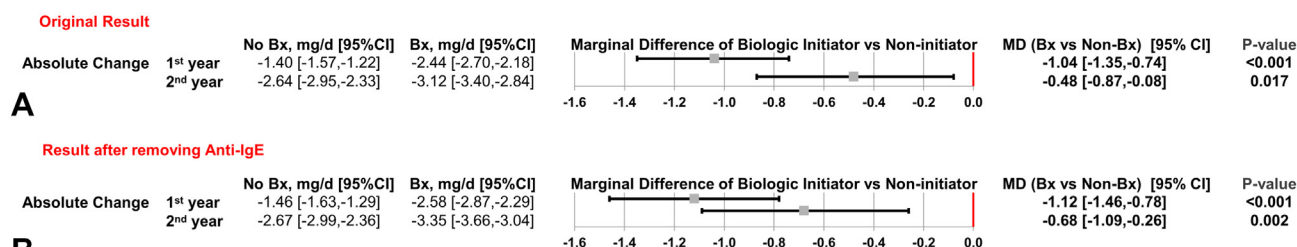


FIGURE 2. Association of biologic (Bx) initiation on daily total oral corticosteroids in first and second years among patients with severe asthma for low-dose and zero-dose outcomes.

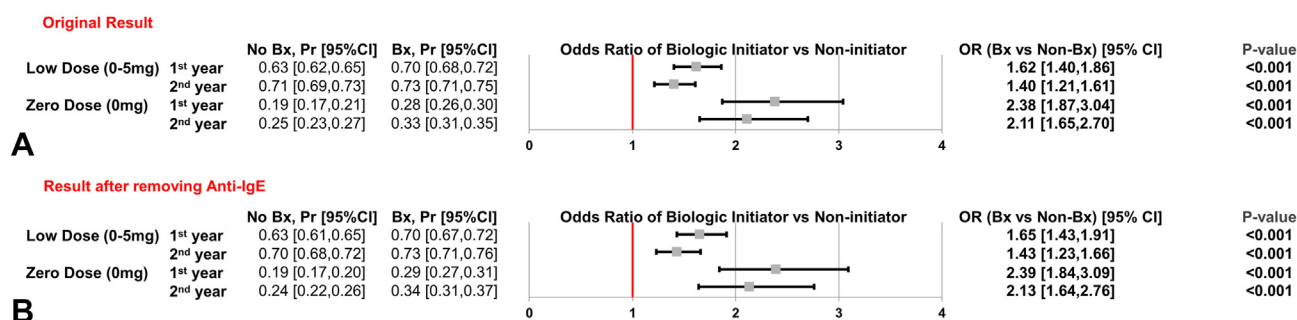


FIGURE 3. Association of biologic (Bx) initiation on daily total oral corticosteroids in first and second years among patients with severe asthma for any reduction and optimal reduction result. *OR*, odds ratio; *Pr*, probability.

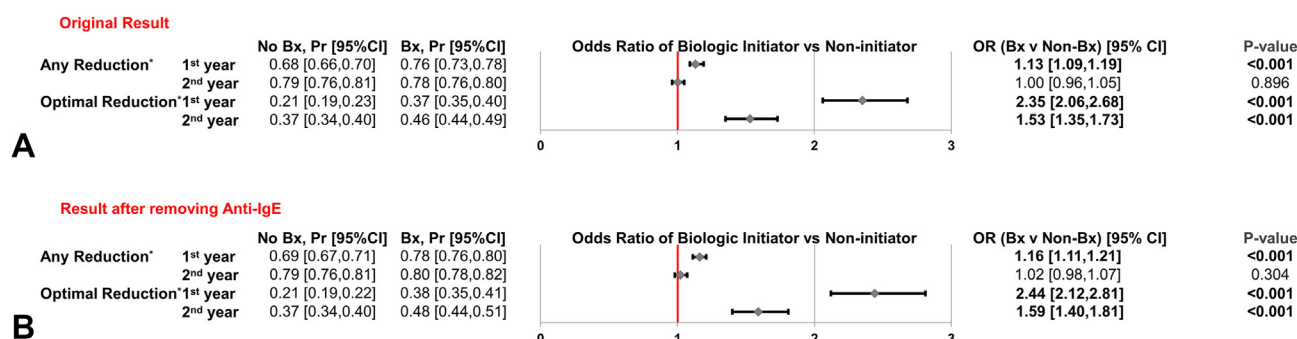


FIGURE 4. Association of biologic (Bx) initiation on daily total oral corticosteroids in first and second years among patients with severe asthma for absolute change. *Any reduction: any reduction in total oral corticosteroid daily dose from baseline (12 months before index date) to first or second year of follow-up. †Optimal reduction: 75% reduction or greater in total oral corticosteroid daily dose from baseline (12 months before index date) to first or second year of follow-up. *OR*, odds ratio; *Pr*, probability.

Robustness and consistency of biologic-associated OCS-weaning effects

As shown in Figure 5 (zero TOCS and optimal reduction) and Figures E8 to E10 (in this article's Online Repository at www.jaci-inpractice.org) (any reduction, low intake, and absolute change), the leave-one-country-out sensitivity analysis revealed persistent and robust findings in biologic-associated OCS reduction, which were not affected by the exclusion of any single country setting. Notably, the pooled ORs of achieving complete cessation were respectively 1.65 (95% CI, 1.58-1.71) and 1.48 (95% CI, 1.40-1.56) in the first and second years of follow-up,

whereas pooled ORs of optimal reduction were 2.25 (95% CI, 2.16-2.34) and 1.52 (95% CI, 1.46-1.58), respectively (Figure 5), all closely aligned with the main analysis.

DISCUSSION

To our knowledge this is the largest real-world study to date on the impact of biologic initiation on TOCS intake in patients with SA, pooling data from a registry of over 20,000 patients with SA across specialist clinics in 20 countries and the United Kingdom's national primary care database. Key distinguishing features of this study include its extended 2-year follow-up and

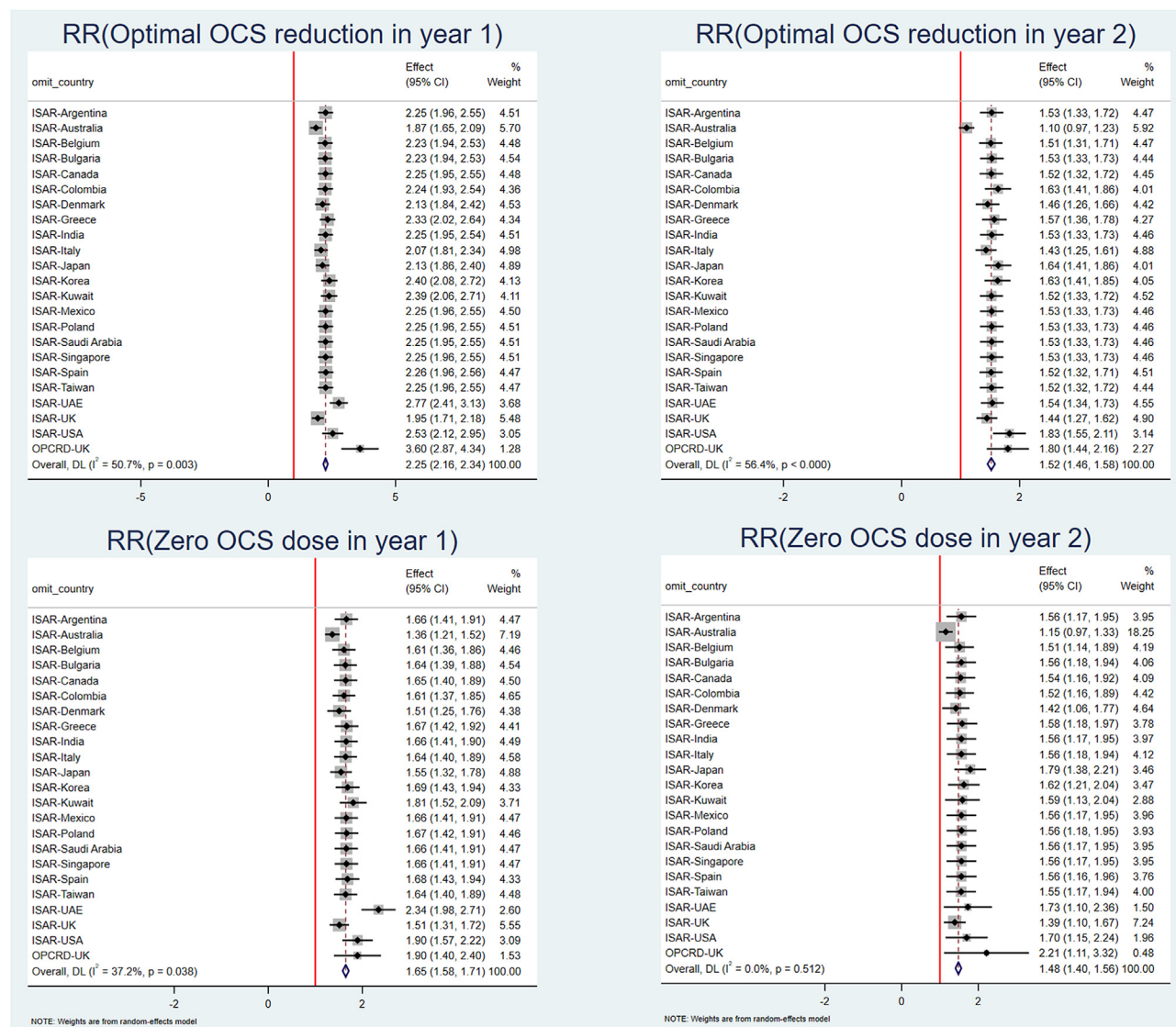


FIGURE 5. Jackknife sensitivity for zero oral corticosteroid (OCS) and optimal reduction (>75%) in years 1 and 2. We tested the stability of outcomes by omitting one country at a time from the analysis. The results show that the outcomes remained stable with the significance of all four outcomes preserved, demonstrating the robustness of findings. *RR*, relative risk.

detailed analyses of multidimensional measures of TOCS change, which provided more comprehensive long-term effect estimates and strengthened the robustness and reliability of the findings. After rigorous PSM and regressions, we demonstrated that biologic initiation was associated with greater reductions in TOCS intake, with more pronounced effect in the first year compared with non-initiators. The effectiveness of biologics was particularly prominent in achieving optimal (>75%) reductions (OR = 2.35 in the first year and OR = 1.53 in the second year) and complete cessation (OR = 2.38 in the first year and OR = 2.11 in the second year). Excluding anti-IgE led to similar results (*P*s for differences: .981 and .959 in the first and second years, respectively). Additionally, the inclusion of a leave-one-country-out sensitivity analysis further strengthened the robustness and reliability of the findings, which showed consistent TOCS reductions with biologic initiation across multiple end points across country settings. These findings lay a robust basis for the

evidence that biologic initiation effectively reduces OCS dependence and exposure in real-world settings.

In 2024, Kyriakopoulos et al⁷⁰ conducted a meta-analysis of 48 RCTs involving 16,350 patients with SA, which reported pooled ORs of 1.68 for greater than 50% TOCS reduction and 1.74 for low TOCS dose (<5 mg/day), whereas 34.67% achieved complete cessation, with biologic initiation. The current first-year findings were similar in achieving a low TOCS dose (OR of 1.62 vs 1.74), and the effect size for cessation was higher (2.38 vs 1.63). Notably, Kyriakopoulos et al primarily analyzed anti-IL-4R α /5/5R α /thymic stromal lymphopoietin agents, whereas 23% of the current biologic initiators received anti-IgE therapy, which has lower efficacy in achieving OCS discontinuation.⁶⁸ Importantly, patients with SA in RCTs may have been subjected to more aggressive OCS weaning and measures to ensure adherence to inhaled corticosteroid regimens compared with real-world settings. Moreover, the recent largest real-world

analysis, GLITTER,³⁵ a large real-world analysis, focused only on patients with SA requiring frequent (≥ 4 /year) OCS bursts or long-term OCS therapy. In comparison, the estimated effect sizes in the current study were also smaller (eg, low OCS dose OR: 1.62 vs 2.48; optimal reduction OR: 2.38 vs 4.01). In addition to the regression toward the mean effect observed in GLITTER, these differences may partially reflect the broader spectrum of disease in the current SA cohort, which involved patients with less OCS dependence, despite some overlap with the patients with severest asthma in GLITTER. GLITTER focused on relative change in 1 year; therefore, given the broader SA cohort and multiple OCS measures over 2 years in this analysis, the current findings are likely more generalizable to the entire SA populations across both primary and secondary care. Our findings were largely consistent with other real-world studies despite their small sample sizes, confirming their robustness and clinical relevance.⁴⁸⁻⁵¹

Although these findings revealed promising OCS-weaning effects of biologics in real-world settings, the comparative reduction in absolute doses remains relatively small over 2 years, and challenges remain in achieving zero use, as indicated by lower ORs compared with RCTs.⁷⁰ For instance, only one third of biologic initiators discontinued OCS by the second year, whereas the average TOCS dose dropped from 6 to 7 mg/day to 3 to 4 mg/day. Potential barriers to complete cessation among biologic initiators include long-standing prescribing practices that over-rely on OCS for SA management and lack of awareness of OCS-related adverse effects. The sensitivity analyses showed moderate heterogeneity in OCS reduction after biologic initiation, because excluding certain countries noticeably shifted point estimates despite consistency in direction, suggesting variations in tapering practices across settings. The absence of standardized strategies for weaning long-term OCS in clinical practice and cautious tapering protocols in clinical trials further complicate efforts to capture corticosteroid-sparing effects fully and the consequent avoidance of OCS-related adverse events in SA.^{21,71,72} Likewise, the high cost of biologics alongside strict reimbursement criteria, as well as insufficient knowledge of biologic therapies outside tertiary care centers, may hamper referrals and access to biologics.

Notably, biologic-associated OCS reduction has been shown to decrease corticosteroid-related adverse events in 61% of patients with SA,⁷³ highlighting the urgent need for more rigorous tapering approaches in addition to biologics. In the 2021 international consensus, experts reaffirmed the importance of establishing tapering strategies for all patients with asthma who were receiving long-term OCS therapy, preferably using personalized approaches.³² As such, future studies should evaluate and implement weaning protocols to achieve biologic-facilitated OCS weaning or elimination. In 2022, Korn et al⁷⁴ reviewed OCS-tapering methods across four RCTs⁷⁵⁻⁷⁸ and one open-label study, PONENTE (benralizumab), the first OCS-tapering trial.⁷⁹ They concluded that stepwise dose reductions every 4 weeks could be achieved while maintaining asthma control. The PONENTE trial demonstrated the superiority of a personalized tapering algorithm to ensure rapid and safe OCS reduction,⁷⁹ highlighting the need for an integrated management approach that combines the prescription of biologic therapies with standardized protocols for OCS reduction.⁸⁰ Thus, real-world application of these or more aggressive approaches merits further investigation.

In the absence of standardized OCS tapering, dose reductions are often guided by physicians based on the perceived likelihood of success. To assess the stability of tapering success, we extended the analysis to the second year. Over 2 years of follow-up, all included patients with SA experienced continuous TOCS reductions, with biologic initiators achieving consistently greater reductions compared with non-initiators. This difference was most prominent in the first year but narrowed in the second year. A possible reason is that responders showed timely improvement in the first year, whereas non-responders in the first year also failed to respond in the second year. In this study, optimal reduction was achieved in 37% of initiators in the first year and 46% in the second year, whereas 22% saw no TOCS reduction. Another factor could be the concern regarding adrenal suppression,²¹ which may be slow to resolve, particularly in high-dose OCS users. Additionally, the differences in treatment strategies, such as optimized inhaled therapy, vaccination, and azithromycin, accompanied by more gradual OCS reduction among non-initiators, could contribute, along with variability in biologic effectiveness across specific drug types. For instance, anti-IL-5/5R α and anti-IL-4R α /13 agents can lead to more rapid and pronounced responses in OCS reduction compared with anti-IgE therapy.^{21,81} Echoing clinical evidence, excluding anti-IgE in our analyses led to similar results, yet with trivially increased effect sizes, likely owing to its lower use. Because of their similar OCS-weaning effects in trials⁷⁰ and our preliminary data (unpublished), the differing distributions of anti-IL-5/5R α and anti-IL-4R α /13 between ISAR and OPCR likely had a minimal impact on the findings.

Future research should investigate OCS reduction patterns across biologic classes while considering biologic treatment switching. The two- to three-fold higher chance of achieving complete cessation or optimal reductions in the first year underscores the potential of biologics in transforming SA management and reducing OCS-related burdens. Conversely, non-users showed slower and less pronounced OCS reductions, particularly in achieving optimal reduction or cessation over 2 years. This highlighted the potential benefit of timely biologic initiation in those likely to benefit, and consistent monitoring within the first 12 months to prevent irreversible adverse effects and improve reversible ones, such as osteoporosis.⁷³ Future research should also focus on evaluating responders and non-responders to asthma biologics, with a clear and standardized definition of non-responders, to understand treatment efficacy and improve patient stratification. A precision medicine approach is critical to optimizing biologic treatment, because our *post hoc* analysis of RCTs highlights significant heterogeneity in treatment responses. Key predictors for reduced severe exacerbations (asthma-related ED visits and/or hospitalizations) with anti-IL-5 treatment included the exacerbation history, BEC, asthma control, and age, whereas predictors for symptom control included BEC and nasal polyps.^{21,82} However, no analysis has specifically focused on OCS reduction. Future studies should develop biologic-specific prediction tools to refine patient selection and maximize treatment efficacy, which should account for cumulative TOCS exposure and multidimensional benefits, including exacerbation prevention, OCS reduction, and improvements in asthma control and lung function.

Our findings convey significant clinical implications. First, as the ultimate aims of OCS tapering, evidence of zero dose and optimal reduction demonstrated the real-world effectiveness of

biologic therapy. Second, as a more sensitive measure to differentiate responders, predictive models of absolute OCS reduction, based on asthma phenotype and endotype, will offer greater discriminative ability for treatment stratification, particularly for biologics with similar overall efficacy but benefitting distinct subgroups. Further research is needed to refine OCS measures and assess their association with long-term outcomes.

In addition to limitations inherent in real-world registry data, this study has several other drawbacks. First, the lack of key criteria for biologic prescription, such as serum IgE and exhaled nitric oxide in OPCRD affected the effectiveness of PSM.⁸³ Second, geographic and socioeconomic variability in biologic initiation were not incorporated into the PSM owing to differences in prescription criteria and inconsistent measurement of socioeconomic status across country settings. Third, asthma control measures varied across countries and tools, and because of data limitations in OPCRD, maintenance and acute OCS bursts were not differentiated. Although TOCS was the more relevant outcome, high-dose ICS were not equated with OCS. Also, phone-only OCS prescriptions may not be fully captured in the datasets. Fourth, heterogeneity within the biologic initiator group, including uneven distribution of biologics (<3% with tezepelumab)⁸⁴ and varying OCS-sparing effects,⁸⁵ were not evaluated, but should be explored in future research. Fifth, potential confounding may have arisen from the methodologic choices, such as using PSM with replacement in both ISAR and OPCRD, in which the number of non-initiators significantly outnumbered biologic initiators in the OPCRD cohort. Data imputation for high-level missing variables may also have introduced residual confounding. Sixth, despite efforts to harmonize methodologies between ISAR and OPCRD analyses, differences in data collection, population characteristics, disease severity, and health care systems might not have accounted fully for the available variables and might have affected the comparability of results. Seventh, data were not specifically collected on the use of infrequent injectable corticosteroids for asthma exacerbations during ED visits and inpatient admissions. Eighth, the physician-driven choice of biologic initiation might have introduced selection bias, because clinicians may prioritize biologics based on expected OCS reduction, although initiators' clinical profiles largely followed guideline recommendations.⁵⁴ Finally, the study did not assess real-world tapering strategies or the effects of OCS reduction on asthma control, exacerbations, or other outcomes; this merits further investigation to confirm tapering success.

Biologic initiation in patients with SA was associated with pronounced and sustained reductions in TOCS intake over time across diverse real-world health care settings, with a two to three times higher chance of achieving optimal reduction and complete cessation. These results highlight the critical need for pragmatic trials and updated clinical guidelines to optimize biologic-facilitated OCS tapering strategies. For patients who are ineligible for biologics, targeted strategies to expand access may include revisiting eligibility criteria and new evaluation methods that account for OCS effects, which can cause corticosteroid-masking effects by suppressing inflammation and related biomarkers to obscure the true disease phenotype, to differentiate OCS-affected patients from true phenotypically

ineligible patients. Future analyses will examine how biologic-mediated OCS reductions reduce adverse health events, further showcasing the benefits of effective OCS-sparing strategies in SA management.

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