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PHARMACOTHERAPY



Asthma biologic trial eligibility and real-world outcomes in the United States

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ABSTRACT

Objective: To compare the outcomes of real-world patients who would have been eligible for asthma biologics to those who would not have been eligible.

Methods: We used data from the OptumLabs Data Warehouse (OLDW) to categorize patients into eligible and ineligible groups based on clinical trials ($n=19$ trials) used for Food and Drug Administration (FDA) approval. We then compared the change in the number of asthma exacerbations before and after biological initiation between the two groups.

Results: The percentage of people who would have been eligible for asthma biologic clinical trials ranged from 0–10.2%. The eligible group had a greater reduction in number of asthma exacerbations compared to the ineligible group based on eligibility criteria from 1 omalizumab trial (1.52, 95% CI 1.25, 1.8 in eligible vs. 0.47, 95% CI 0.43, 0.52 in ineligible) and from 1 dupilumab trial (1.6, 95% CI 0.92, 2.28 in eligible vs. 0.52, 95% CI 0.38, 0.65 ineligible). Notably, 15 of the 19 trials had fewer than 11 eligible people, limiting additional comparisons.

Conclusions: Fewer than 1 in 10 people in the United States treated with asthma biologics would have been eligible to participate in the trial for the biologic they used. Where comparisons could be made, trial eligible people have a greater reduction in exacerbations.

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Introduction

Asthma is a common chronic disease affecting 7.7% of adults and 7.5% of children in the United States (1). The 5–10% of asthma patients who have severe asthma account for approximately 50% of all asthma-associated costs (2). People with severe asthma not achieving control with first-line medications may be treated with asthma biologics (omalizumab, mepolizumab, reslizumab, benralizumab, and dupilumab). While only 3 out of 1000 people with asthma use biologics (3), they are an important treatment option for people with severe asthma (4,5).

Randomized controlled trials (RCTs) conducted for the drug approval process have inclusion and exclusion criteria that can be used to identify the target patient population. However, the results of RCTs may not apply to many people who present for care in clinical practice as they may not meet the inclusion/exclusion criteria used for the RCT. In a systematic review of 52 studies that examined the external

validity of RCTs in cardiology, mental health, and oncology, 37 studies found that RCTs were not representative of the patient population (6). One study that evaluated the clinical trial criteria for asthma biologics found that 65–76% of severe patients would not have been eligible for any of the three asthma biologics (reslizumab, omalizumab, mepolizumab) based on their RCT inclusion criteria (7). Other studies have found even lower percentages of patients who would qualify for a biologic under trial inclusion and exclusion criteria (8–10). Clinical trials have also failed to recruit patients who match the diversity of people with asthma. People who are black, smoke, or are obese are underrepresented in asthma biologic medication trials, further contributing to a lack of external validity (11). The most common characteristics that would have excluded real-world asthma patients from clinical trials included the following: less than 1 exacerbation requiring oral corticosteroids and ER/hospitalization in the past year (7), insufficient

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airflow reversibility, past smoking history, and the presence of comorbidities such as COPD (12).

The use of real-world evidence (RWE) has become increasingly used to assess drug effectiveness and safety. With the enactment of the 21st Century Cures Act in 2016, the FDA committed to using RWE as defined by sources other than RCTs such as observational data from electronic health records, disease registries, and billing records (13,14).

While several previous research studies suggest that people with severe asthma who use asthma biologics would not have qualified for the pivotal studies used to approve the drugs, little is known if trial eligibility is associated with different treatment outcomes. This study examines outcomes in people treated with asthma biologics in clinical practice and compares people who would have been eligible for pivotal clinical trials with people who would have been ineligible. We hypothesize that individuals with severe asthma who do not meet trial eligibility criteria have a lower treatment response to asthma biologics compared to people who meet trial eligibility.

Materials and methods

Overall design

We conducted a retrospective observational study using the OptumLabs Data Warehouse (OLDW) for the years 2003–2019 to identify people with asthma who used an asthma biologic. We stratified patients into trial eligible and ineligible groups. Next, we compared asthma exacerbations before and after biological use. This study was exempt from review by our Institutional Review Board as the data were preexisting and de-identified. The study is reported to be consistent with the 22 items detailed in the STROBE statement.

Study population

We used the OLDW, a database of healthcare claims for over 200 million privately insured and Medicare Advantage enrollees (15), to build the cohort by starting with all beneficiaries who met a modified version of the Healthcare Effectiveness Dataset Information Set (HEDIS) criteria for persistent asthma who had at least 6 months of continuous enrollment in both medical and pharmacy coverage between 2003 and 2019 prior to their index biologic use. We modified HEDIS criteria by using a rolling year rather than a calendar year and by including people with comorbid COPD. We then eliminated patients who did not have

at least 6 months of continuous enrollment after index biologic use (cohort selection flow diagram is given in Figure 1).

Data definitions

We determined the clinical trial criteria by using the listed inclusion and exclusion criteria of a given trial registered on www.clinicaltrials.gov. The pivotal trials were identified in the Clinical Studies section of the label for each biologic. The trials included in the label were then identified on the www.clinicaltrials.gov website by conducting an advanced search for “[biologic name]” and filtering for completed studies with results. The number of subjects in each trial from the label was then matched to the number of subjects on www.clinicaltrials.gov to ensure that the correct trial was referenced.

Trial eligibility was determined by applying the trial inclusion and exclusion criteria to real-world data (see eTable 1 (supplementary material) for trial inclusion and exclusion criteria). Eligibility was determined based on the following five characteristics and screened in the following order: age, number of exacerbations, comorbid conditions, smoking status, and

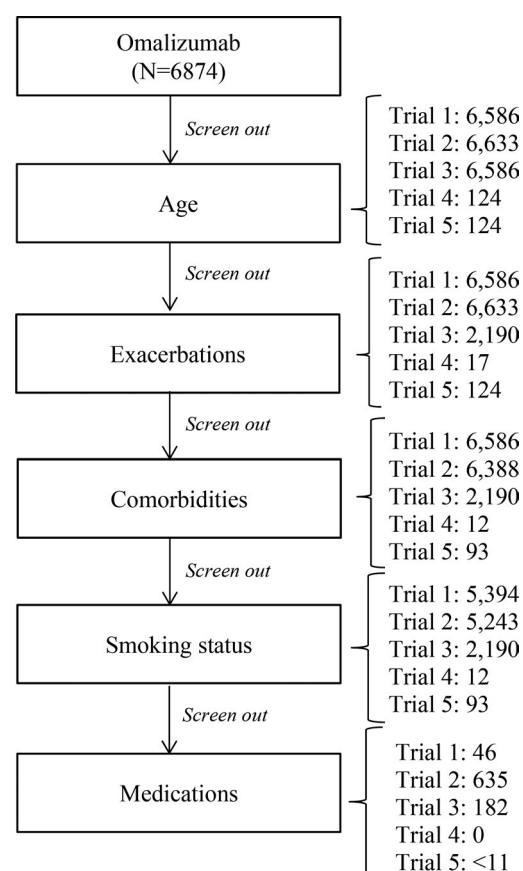


Figure 1. Eligibility by trial criteria.

medications. The order selected was based on most available and reliable to least available and reliable data to avoid preemptively screening out individuals who have incomplete data. The percent of eligible individuals was calculated after each eligibility criterion was applied. Eligibility was also calculated for every trial for each corresponding biologic for people who actually used each medicine in the cohort (i.e. omalizumab users were tested for eligibility for the 5 omalizumab trials).

Asthma exacerbations were defined as any of the following: hospitalization with a primary diagnosis of asthma or in a secondary position with a respiratory diagnosis in the first position, emergency department (ED) visit with a primary diagnosis of asthma, or a pharmacy fill for a systemic corticosteroid within 1 month of an outpatient visit with a primary diagnosis of asthma. We allowed each patient to be credited with no more than 1 exacerbation in a 30-day rolling period to avoid double-counting of a single episode that may span multiple ED visits, hospitalizations, or outpatient visits and corticosteroid fills. We then assessed for comorbid conditions that trials used as exclusionary criteria using diagnostic codes for each condition. This included smoking status, other active lung disease (e.g. COPD), and malignancy (see eTables 1 and 2, [supplementary material](#)) Smoking status was assessed in our data set using diagnostic codes and could not capture current versus past smoking or number of pack-years. Current asthma medications were sorted into long-acting beta agonists (LABA), oral corticosteroids, low dose inhaled corticosteroids (ICS), medium dose ICS, and high dose ICS (see eTable 3 for ICS definitions, [supplementary material](#)). A medication was considered current at the time of biologic initiation if it was within the prescription's count days supply from the prescription claim (e.g. if biologic initiation fell within 30 days after the fill date of a prescription fill with a 30-day supply).

Outcomes

The primary asthma outcome used for this study is the absolute change in number of asthma exacerbations (AE), as defined in the section above, before and after initiation of an asthma biologic. The number of AEs were counted 12 months pre- and post-index date in which index date was defined as the start of a biologic. We defined improvement in AEs as a reduction in number of AEs (i.e. a higher pre-biologic AE count than post-biologic AE count). Therefore, a positive number for AE change means that the person

had more AEs in the period before starting biologic compared to after starting biologic. For example, a person who had 3 AEs before starting and 2 AEs after would have a score of 1.

Statistical analysis

The study population was divided into cohorts of eligible and ineligible patients according to the inclusion and exclusion criteria for each trial cited in each biologic FDA label. We examined the average number of exacerbations in a 12-month period before and after the start of each biologic for treatment eligible and ineligible groups. Notably, only the people who had 12 months of pre- and post-index coverage were included in the analysis of exacerbation change. We then calculated the absolute change in the number of exacerbations with a 95% confidence interval. When fewer than 11 individuals were eligible in a specific category, an inexact number was reported in our results using > or < signs, following the data privacy specifications of Optum Labs to keep the data deidentified.

Results

Overall study population

Our overall study population was 9,783 people after we excluded people who may have used the biologics of interest for indications other than asthma: atopic dermatitis ($n=3,941$), urticaria ($n=1,307$), or both atopic dermatitis and urticaria ($n=445$). Out of this overall study population, we had 6,874 people taking omalizumab, 1,382 taking mepolizumab, 1,039 taking dupilumab, 378 taking benralizumab, and 110 taking reslizumab. The cohort ranged in age between means of 47.3 to 64.1 years old and was 57–65% female. Most were nonsmokers and did not have concurrent COPD or malignancies (see [Table 1](#)). Depending on the biologic, people were either on no asthma medications 30 days prior to starting the biologic or were only on ICS LABA with between 27–45% having pharmacy claims for high dose ICS LABA ([Table 1](#)).

Eligibility for asthma biologic clinical trials

Patients rarely met trial inclusion and exclusion criteria for 5 biologics in the 19 trials we examined, with omalizumab having the highest percent eligible in any trial (10.2%), followed by dupilumab (6.3%). Trial eligibility remained low when split by each trial

Table 1. Patient characteristics.

	Benralizumab (N = 378)	Dupilumab (N = 1,039)	Mepolizumab (N = 1,382)	Omalizumab (N = 6,874)	Reslizumab (N = 110)
On Treatment for 6 months+	158 (41.80%)	338 (32.53%)	779 (56.37%)	4,093 (59.54%)	66 (60.00%)
On Treatment for 12 months+	54 (14.29%)	97 (9.34%)	463 (33.50%)	2,627 (38.22%)	43 (39.09%)
12+ months of coverage Post-Index	285 (75.40%)	316 (30.41%)	952 (68.89%)	4,947 (71.97%)	83 (75.45%)
12+ months of coverage Pre-Index	341 (90.21%)	877 (84.41%)	1,160 (83.94%)	5,551 (80.75%)	92 (83.64%)
Age					
Mean (SD)	64.1 (13.0)	52.5 (15.4)	57.3 (14.6)	47.3 (16.1)	58.1 (12.8)
Median	67.0	54.0	59.0	49.0	59.0
Age group					
0–5	0	0	0	<11	0
6–11	0	0	0	>72	0
12–17	<11	17 (1.64%)	17 (1.23%)	359 (5.22%)	0
18–64	>140	787 (75.75%)	892 (64.54%)	5,522 (80.33%)	71 (64.55%)
65+	226 (59.79%)	235 (22.62%)	473 (34.23%)	906 (13.18%)	39 (35.45%)
Gender					
Female	246 (65.08%)	592 (56.98%)	852 (61.65%)	4,274 (62.18%)	72 (65.45%)
Smoking	157 (41.53%)	303 (29.16%)	465 (33.65%)	1,284 (18.68%)	31 (28.18%)
COPD	213 (56.35%)	337 (32.44%)	619 (44.79%)	2,511 (36.53%)	53 (48.18%)
Cancer	56 (14.81%)	113 (10.88%)	165 (11.94%)	649 (9.44%)	<11
Other lung disease	258 (68.25%)	508 (48.89%)	819 (59.26%)	2,972 (43.24%)	64 (58.18%)
Current asthma controller					
Medications					
None	164 (43.39%)	526 (50.63%)	580 (41.97%)	3,675 (53.46%)	46 (41.82%)
ICS Only	27 (7.14%)	86 (8.28%)	>110	508 (7.39%)	<11
OCS only	<11	<11	12 (0.87%)	67 (0.97%)	0
ICS + OCS	0	<11	<11	12 (0.17%)	<11
ICS LABA	183 (48.41%)	406 (39.08%)	654 (47.32%)	2,559 (37.23%)	52 (47.27%)
ICS LABA + OCS	<11	<11	12 (0.87%)	53 (0.77%)	<11
Current ICS	21 (5.56%)	88 (8.47%)	109 (7.89%)	229 (3.33%)	<11
Low Dose					
Current ICS	16 (4.23%)	40 (3.85%)	85 (6.15%)	384 (5.59%)	12 (10.91%)
Medium Dose					
Current ICS	13 (3.44%)	40 (3.85%)	50 (3.62%)	182 (2.65%)	<11
High Dose					
Current ICS/LABA Low Dose	<11	<11	<11	74 (1.08%)	0
Current ICS/LABA Medium Dose	43 (11.38%)	81 (7.80%)	135 (9.77%)	746 (10.85%)	<11
Current ICS/LABA High Dose	144 (38.10%)	337 (32.44%)	540 (39.07%)	1,836 (26.71%)	49 (44.55%)
Current OCS	<11	21 (2.02%)	27 (1.95%)	132 (1.92%)	<11
Current Reliever	151 (39.95%)	313 (30.13%)	513 (37.12%)	2,430 (35.35%)	39 (35.45%)
Number of Exacerbations in 12 Mths Pre-Index					
None	178 (47.09%)	666 (64.10%)	567 (41.03%)	3,212 (46.73%)	45 (40.91%)
1	86 (22.75%)	189 (18.19%)	332 (24.02%)	1,744 (25.37%)	19 (17.27%)
2 or greater	114 (30.16%)	184 (17.71%)	483 (34.95%)	1,918 (27.90%)	46 (41.82%)

Table 2. Eligibility by biologic trial.

	Omalizumab		Mepolizumab		Reslizumab		Benralizumab		Dupilumab	
	Eligible	Ineligible	Eligible	Ineligible	Eligible	Ineligible	Eligible	Ineligible	Eligible	Ineligible
Any trial	805	6,069	<11	>1,371	<11	>99	<11	>367	62	977
Trial 1	46	6,828	0	1,382	<11	>99	<11	>367	62	977
Trial 2	635	6,239	0	1,382	<11	>99	<11	>367	<11	<1,028
Trial 3	182	6,692	<11	>1,371	<11	>99	<11	>367	0	1,039
Trial 4	0	6,874	0	1,382	<11	>99				
Trial 5	<11	> 6,863								

for each biologic. The range of eligibility by trial was 0–9.2% for omalizumab, 0–6.0% dupilumab, 0–<0.8% for mepolizumab, 0–<0.8% for benralizumab, and <0.8% for reslizumab (see Table 2).

Depending on the biologic, the inclusion criteria of preexisting medications and/or exacerbations (i.e. patients having too few exacerbations to have qualified

for the study) were the criteria that led to the largest decreases in eligibility (see eFigure 1). For omalizumab, medications were the driving characteristic that screened out most patients. The omalizumab trial with the highest percent eligible demonstrated 76% eligibility prior to medication screen out and 9.2% after medication screen out. For dupilumab,

exacerbations and preexisting medications both contributed to large declines in eligibility. The dupilumab trial with the highest percent eligible demonstrated 98.0% eligibility prior to considering exacerbations and 34.0% afterwards. Prior to considering medications, the dupilumab trial had 10.4% eligible, which decreased to 6.0% afterwards.

While mepolizumab had the second highest number of total patients after omalizumab, it yielded a lower percentage eligible than dupilumab. Unlike with omalizumab and dupilumab, the greatest eligibility decline for eligibility for mepolizumab trials occurred after considering the exclusion criteria of comorbidities: 100% prior to consideration and 36.5% afterwards for trial 3, the trial with the highest number eligible (see eFigure 1).

Asthma outcomes in patients eligible and ineligible in clinical trials

Trial eligible and ineligible groups both demonstrated a reduction in 12-month asthma exacerbations after starting the biologic compared to the 12-month period prior to starting the asthma biologic. The level of reduction varied depending on the biologic and trial. For omalizumab, trial 3 yielded statistically significant decreases in asthma exacerbations for the eligible group, 1.52 (95% CI: 1.25, 1.8), and 0.47 (95% CI: 0.43, 0.52) for the ineligible group. Dupilumab trial 1 also demonstrated a greater decrease in number of asthma exacerbations for the eligible group in trial 1 [1.6 (CI 0.92, 2.28)] compared to the ineligible group [0.52 (CI 0.38, 0.65)]. Other differences between the trial eligible and ineligible groups were not significant (see Table 3), and only 15 of the 19 trials had >11 people in the eligible category for comparison.

The greater decreases in asthma exacerbations in the treatment eligible compared to the ineligible group were present as well when eligibility was determined by each screening characteristic. In particular, when eligibility was determined by the number of existing exacerbations, the group eligible for omalizumab demonstrated a greater decrease in exacerbations compared to the ineligible group across all trials, with the greatest difference seen in Trial 3 [1.52 (95% CI 1.44, 1.61) vs. -0.05 (95% CI -0.08, -0.01)]. A similar pattern was seen between the eligible and ineligible groups for dupilumab, with the greatest difference seen in trials 1 and 2 [95% CI 1.86 (1.55, 2.18) vs -0.02 (95% CI -0.05, 0)] (see Table 4).

Discussion

The percentage of people who used asthma biologics in US clinical practices who would have been eligible for an asthma biologic clinical trial is low. The low trial eligibility suggests that providers rely on characteristics other than those in trial eligibility criteria to determine whether to initiate an asthma biologic. The low trial eligibility also raises concerns about the generalizability of asthma biologic trial outcomes to the people who are currently using them in the US. We were able to test the concern for generalizability in only a few comparisons due to so few people fitting into the eligible category for most trials. In the comparisons we were able to test, we found that people eligible for trials had better asthma outcomes.

Our findings of low eligibility are consistent with prior research, which demonstrated that eligibility varied between 6% and 20% depending on biologic and methodology. The study with the largest cohort of 749 people determined eligibility based on

Table 3. Absolute reduction in exacerbations by biologic trial.

	Omalizumab		Mepolizumab		Reslizumab		Benralizumab		Dupilumab	
	Eligible (CI)	Ineligible (CI)	Eligible (CI)	Ineligible (CI)	Eligible (CI)	Ineligible (CI)	Eligible (CI)	Ineligible (CI)	Eligible (CI)	Ineligible (CI)
Trial 1	0.26 (-0.16, 0.68)	0.51 (0.46, 0.55)	~	0.87 (0.77, 0.97)	5 (5, 5)	0.85 (0.51, 1.2)	2.6 (1.92, 3.28)	0.83 (0.67, 1)	1.6 (0.92, 2.28)	0.49 (0.36, 0.63)
Trial 2	0.52 (0.36, 0.68)	0.5 (0.46, 0.55)	~	0.87 (0.77, 0.97)	5 (5, 5)	0.85 (0.51, 1.2)	2.6 (1.92, 3.28)	0.83 (0.67, 1)	~	0.52 (0.38, 0.65)
Trial 3	1.52 (1.25, 1.8)	0.47 (0.43, 0.52)	0.2 (-3.13, 3.53)	0.87 (0.77, 0.97)	5 (5, 5)	0.85 (0.51, 1.2)	2.67 (-4.5, 9.84)	0.85 (0.68, 1.01)	~	0.52 (0.38, 0.65)
Trial 4	~	0.51 (0.46, 0.55)	~	0.87 (0.77, 0.97)	5 (5, 5)	0.85 (0.51, 1.2)				
Trial 5	2 (2, 2)	0.51 (0.46, 0.55)								

Table 4. Absolute reduction in exacerbations by inclusion/exclusion criteria*.

Drug	Criteria	Status	Trial 1	Trial 2	Trial 3	Trial 4	Trial 5
Omalizumab	Age	Ineligible	0.59 (0.41, 0.76)	0.58 (0.39, 0.76)	0.59 (0.41, 0.76)	0.5 (0.46, 0.55)	0.5 (0.46, 0.55)
		Eligible	0.5 (0.46, 0.55)	0.5 (0.46, 0.55)	0.5 (0.46, 0.55)	0.76 (0.39, 1.13)	0.76 (0.39, 1.13)
	Comorbidities	Ineligible	0 (0, 0)	1.09 (0.75, 1.44)	0 (0, 0)	0.57 (0.51, 0.63)	0.57 (0.51, 0.63)
		Eligible	0.51 (0.46, 0.55)	0.49 (0.44, 0.53)	0.51 (0.46, 0.55)	0.43 (0.38, 0.49)	0.43 (0.38, 0.49)
	Exacerbations	Ineligible	0 (0, 0)	0 (0, 0)	-0.05 (-0.08, -0.01)	0.47 (0.42, 0.51)	0 (0, 0)
		Eligible	0.51 (0.46, 0.55)	0.51 (0.46, 0.55)	1.52 (1.44, 1.61)	0.76 (0.6, 0.92)	0.51 (0.46, 0.55)
	Current medication	Ineligible	0.51 (0.46, 0.55)	0.5 (0.46, 0.55)	0.51 (0.46, 0.55)	0.51 (0.46, 0.55)	0.51 (0.47, 0.55)
		Eligible	0.3 (-0.13, 0.73)	0.53 (0.39, 0.66)	0.48 (0.33, 0.63)	0.48 (0.33, 0.63)	0.31 (-0.14, 0.76)
	Smoking status	Ineligible	0.6 (0.5, 0.7)	0.6 (0.5, 0.7)	0 (0, 0)	0 (0, 0)	0 (0, 0)
		Eligible	0.48 (0.44, 0.53)	0.48 (0.44, 0.53)	0.51 (0.46, 0.55)	0.51 (0.46, 0.55)	0.51 (0.46, 0.55)
Mepolizumab	Age	Ineligible	0.91 (0.72, 1.09)	0 (0, 0)	0 (0, 0)	0.87 (0.77, 0.97)	
		Eligible	0.84 (0.72, 0.96)	0.87 (0.77, 0.97)	0.87 (0.77, 0.97)	0 (0, 0)	
	Comorbidities	Ineligible	0.94 (0.8, 1.08)	0.93 (0.79, 1.06)	0.93 (0.79, 1.06)	0 (0, 0)	
		Eligible	0.74 (0.6, 0.89)	0.76 (0.61, 0.91)	0.76 (0.61, 0.91)	0.87 (0.77, 0.97)	
	Exacerbations	Ineligible	0 (0, 0)	0.16 (0.1, 0.22)	0 (0, 0)	0.16 (0.1, 0.22)	
		Eligible	0.87 (0.77, 0.97)	2.22 (2.03, 2.4)	0.87 (0.77, 0.97)	2.22 (2.03, 2.4)	
	Current medication	Ineligible	0.87 (0.77, 0.97)	0.87 (0.77, 0.97)	0.88 (0.78, 0.98)	0.87 (0.77, 0.97)	
		Eligible	0 (0, 0)	0 (0, 0)	0.29 (-0.65, 1.23)	0 (0, 0)	
	Smoking status	Ineligible	0.9 (0.71, 1.09)	0 (0, 0)	0.9 (0.71, 1.09)	0 (0, 0)	
		Eligible	0.85 (0.73, 0.97)	0.87 (0.77, 0.97)	0.85 (0.73, 0.97)	0.87 (0.77, 0.97)	
Reslizumab	Age	Ineligible	1 (-1.25, 3.25)	1 (-1.25, 3.25)	1 (-1.25, 3.25)	1 (-1.25, 3.25)	
		Eligible	0.91 (0.53, 1.28)	0.91 (0.53, 1.28)	0.91 (0.53, 1.28)	0.91 (0.53, 1.28)	
	Comorbidities	Ineligible	0.91 (0.5, 1.32)	0.91 (0.5, 1.32)	0.91 (0.5, 1.32)	0.91 (0.5, 1.32)	
		Eligible	0.92 (0.18, 1.65)	0.92 (0.18, 1.65)	0.92 (0.18, 1.65)	0.92 (0.18, 1.65)	
	Exacerbations	Ineligible	-0.04 (-0.11, 0.04)	-0.04 (-0.11, 0.04)	-0.04 (-0.11, 0.04)	-0.04 (-0.11, 0.04)	
		Eligible	1.58 (1.05, 2.1)	1.58 (1.05, 2.1)	1.58 (1.05, 2.1)	1.58 (1.05, 2.1)	
	Current medication	Ineligible	0.83 (0.48, 1.18)	0.83 (0.48, 1.18)	0.83 (0.48, 1.18)	0.83 (0.48, 1.18)	
		Eligible	2.67 (-3.58, 8.92)	2.67 (-3.58, 8.92)	2.67 (-3.58, 8.92)	2.67 (-3.58, 8.92)	
	Smoking status	Ineligible	1.33 (0.55, 2.11)	1.33 (0.55, 2.11)	1.33 (0.55, 2.11)	1.33 (0.55, 2.11)	
		Eligible	0.72 (0.32, 1.12)	0.72 (0.32, 1.12)	0.72 (0.32, 1.12)	0.72 (0.32, 1.12)	
Benralizumab	Age	Ineligible	0.9 (0.48, 1.31)	0.9 (0.48, 1.31)	0.88 (0.47, 1.29)		
		Eligible	0.86 (0.68, 1.05)	0.86 (0.68, 1.05)	0.87 (0.68, 1.05)		
	Comorbidities	Ineligible	0.9 (0.69, 1.11)	0.9 (0.69, 1.11)	0.88 (0.68, 1.09)		
		Eligible	0.79 (0.5, 1.08)	0.79 (0.5, 1.08)	0.82 (0.51, 1.13)		
	Exacerbations	Ineligible	0.21 (0.14, 0.29)	0.21 (0.14, 0.29)	-0.04 (-0.08, 0)		
		Eligible	2.65 (2.31, 2.99)	2.65 (2.31, 2.99)	1.85 (1.6, 2.1)		
	Current medication	Ineligible	0.84 (0.64, 1.03)	0.84 (0.64, 1.03)	0.87 (0.69, 1.04)		
		Eligible	0.94 (0.61, 1.27)	0.94 (0.61, 1.27)	0.88 (0.08, 1.67)		
	Smoking status	Ineligible	*	*	*		
		Eligible	0.87 (0.7, 1.04)	0.87 (0.7, 1.04)	0.87 (0.7, 1.04)		
Dupilumab	Age	Ineligible	-0.25 (-1.05, 0.55)	0 (0, 0)	0 (0, 0)		
		Eligible	0.53 (0.39, 0.67)	0.52 (0.38, 0.65)	0.52 (0.38, 0.65)		
	Comorbidities	Ineligible	0.47 (0.33, 0.62)	0.47 (0.33, 0.62)	0.76 (0.55, 0.97)		
		Eligible	1.31 (0.85, 1.76)	1.31 (0.85, 1.76)	0.14 (0.03, 0.25)		
	Exacerbations	Ineligible	-0.02 (-0.05, 0)	-0.02 (-0.05, 0)	0 (0, 0)		
		Eligible	1.86 (1.55, 2.18)	1.86 (1.55, 2.18)	0.52 (0.38, 0.65)		
	Current medication	Ineligible	0.49 (0.36, 0.63)	0.52 (0.38, 0.65)	0.52 (0.38, 0.65)		
		Eligible	1.6 (0.92, 2.28)	0 (0, 0)	0 (0, 0)		
	Smoking status	Ineligible	0.49 (0.35, 0.63)	0.49 (0.35, 0.63)	0.69 (0.5, 0.87)		
		Eligible	1.33 (0.95, 1.72)	1.33 (0.95, 1.72)	0.12 (-0.01, 0.24)		

Bolded all comparisons where 95% CI do not overlap for comparison between ineligible and eligible, except when there is 0 (0,0) on one side of the comparison.

*None were ineligible for benralizumab based only on smoking status.

participant questionnaire responses and found that only 6% of respondents with asthma and currently on treatment would have been eligible (8). Unlike this study, eligibility was determined using self-provided pulmonary function tests, chest CT, eosinophil and immunoglobulin E counts, variables that we did not consider. Other studies similarly found low rates of trial eligibility among people treated in real-world settings: Pahus et al. analyzed 303 people with severe asthma from France and Brown et al. analyzed 342 severe asthma patients from the United Kingdom (9,10). Another study found a similar low rate of

eligibility in a population of 670 people from Canada, France, Germany, and the United States (7). Notably, this study determined eligibility based on data from electronic health records (EHR) as well as one in-person visit, allowing for collection of data not available in the EHR. All together, our study joins others in finding that most people using asthma biologics in clinical practice would not fit eligibility criterion for the trials that supported their approval.

We performed analyses on each eligibility criteria to determine the key differences between people treated on trials and in the real-world data set. We

found that the number of exacerbations and/or current medications were responsible for screening out most patients across asthma biologics. Most people do not have more than two exacerbations before starting biologics. In addition, many people did not have recent claims for other asthma controller medications prior to initiating asthma biologics. Providers may not have an effective way of determining whether patients are filling their medications before determining failure and therefore deciding on progression to an asthma biologic. Unlike in a clinical trial setting, real-world patients may not consistently take their ICS. In real-world data, ICS adherence stays about the same before and after biologic initiation (16), whereas ICS adherence may increase in trial settings compared to prior non-trial settings. Therefore, there may be a differential increase in ICS use in clinical trials which could account for differences seen in RWE.

Although the number of eligible patients was low for each biologic, statistically significant differences in outcomes between eligible and ineligible groups were present for omalizumab and dupilumab. For both biologics, the eligible group consistently performed better than the ineligible group across all trials, a pattern that appears to be driven by the exacerbation inclusion criterion. This is seen when comparing omalizumab trials 2 and 3, where no difference in outcomes are seen in trial 2 (no eligibility criteria requiring asthma exacerbations) and a larger exacerbation reduction seen in trial 3 for eligible patients, which had to have at least 1 prior exacerbation. Though the ineligible group had a smaller reduction in exacerbations, they also had fewer exacerbations at baseline. Therefore, the opportunity for the ineligible group to reduce their exacerbations is also limited and cannot be used to conclude that the ineligible group does not benefit from biologic use. Given these findings, the ability to base prescribing and coverage decisions of asthma biologics on baseline exacerbations is limited. The benefit that the ineligible group may experience from biologics is unknown at this time. Given the high cost of asthma biologics, future research using additional outcomes besides exacerbations is needed to guide policy and help define the patient population that will most benefit.

Our study has some important limitations to consider. First, our findings likely overestimate the true eligibility of asthma biologics as we did not account for pulmonary function tests, eosinophil levels, and other laboratory results that would have screened out additional people from being eligible to participate

in clinical trials. Also, we did not include every comorbidity listed in every trial (eTable 1, [supplementary material](#)) and were unable to capture the smoking history variable in the same detail as it was used for trial eligibility. Furthermore, given the limited number of people who met trial eligibility, our conclusions on the outcomes of trial eligible and ineligible groups are limited to omalizumab and dupilumab. Therefore, the findings cannot necessarily be generalized to other asthma biologics. Finally, we defined our outcomes as the number of exacerbations. This does not account for other metrics that can be used to assess the effectiveness of asthma medications such as quality of life parameters (e.g. number of missed school and work days).

Strengths of our study include a cohort that includes people across multiple providers and health systems, and the largest sample size to-date to address questions related to the generalizability of asthma biologic trial outcomes. Furthermore, we believe that this study is the first to compare the outcomes between trial eligible and ineligible patients for asthma biologics. This allows us to better understand whether people who would have been ineligible for clinical trials may have different outcomes than people who would have qualified for the trials.

Conclusion

Most people using asthma biologics in the US would have been ineligible for the biologic clinical trials leading to their approval. The outcomes between asthma biologic trial eligible and ineligible patients cannot be compared for some biologics due to low percentage of eligibility. Based solely on number of exacerbations as an outcome and seen only in 2 of the trials we examined, trial eligible patients appear to benefit more from biologics, though additional outcomes would need to be assessed to understand the benefits for the ineligible group. Additional research is needed to understand how RWE for asthma biologics can inform prescribing choices.

Declaration of interest

None of the authors report a conflict of interest.

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