Comparative effectiveness of omalizumab, mepolizumab, and dupilumab in asthma: A target trial emulation

Ayobami T. Akenroye, MBChB, MPH, PhD,[a,b,c] Jodi B. Segal, MD, MPH,[c,d,e] Guohai Zhou, PhD,[f] Dinah Foer, MD,[a,g] Lily Li, MD,[a] G. Caleb Alexander, MD, MS,[c,d,e] Corinne A. Keet, MD, PhD,[h] and John W. Jackson, ScD[c,e,i,j] *Boston, Mass; Baltimore, Md; and Chapel Hill, NC*

Background: Multiple mAbs are currently approved for the treatment of asthma. However, there is limited evidence on their comparative effectiveness.
Objective: Our aim was to compare the effectiveness of omalizumab, mepolizumab, and dupilumab in individuals with moderate-to-severe asthma.
Methods: We emulated a hypothetical randomized trial using electronic health records from a large US-based academic health care system. Participants aged 18 years or older with baseline IgE levels between 30 and 700 IU/mL and peripheral eosinophil counts of at least 150 cells/μL were eligible for study inclusion. The study period extended from March 2016 to August 2021. Outcomes included the incidence of asthma-related exacerbations and change in baseline FEV_1 value over 12 months of follow-up.
Results: In all, 68 individuals receiving dupilumab, 68 receiving omalizumab, and 65 receiving mepolizumab met the inclusion criteria. Over 12 months of follow-up, 31 exacerbations occurred over 68 person years (0.46 exacerbations per person year) in the dupilumab group, 63 over 68 person years (0.93 per person year) in the omalizumab group, and 86 over 65 person years (1.32 per person year) in the mepolizumab group (adjusted incidence rate ratios: dupilumab vs mepolizumab, 0.28 [95% CI = 0.09-0.84]; dupilumab vs omalizumab, 0.36 [95% CI = 0.12-1.09]; and omalizumab vs mepolizumab, 0.78 [95% CI = 0.32-1.91]). The differences in the change in FEV_1 comparing patients who received the different biologics were as follows: 0.11 L (95% CI = –0.003 to 0.222 L) for dupilumab versus mepolizumab, 0.082 L (95% CI –0.040 to 0.204 L) for dupilumab versus omalizumab, and 0.026 L (95% CI –0.083 to 0.140 L) for omalizumab versus mepolizumab.
Conclusions: Among patients with asthma and eosinophil counts of at least 150 cells/μL and IgE levels of 30 to 700 kU/L, dupilumab was associated with greater improvements in exacerbation and FEV_1 value than omalizumab and mepolizumab. (J Allergy Clin Immunol 2023;151:1269-76.)

Key words: *Asthma, comparative effectiveness, mAbs, target trial emulation, dupilumab, mepolizumab, omalizumab, eosinophilic, allergic*

In December 2021, a sixth mAb, or "biologic," was approved for the treatment of severe asthma. However, head-to-head comparisons of the previously approved biologics are still lacking, thus limiting opportunities to optimize patient selection for these costly therapies.[1] For individuals who meet the prescribing criteria for only 1 of these therapies, the choice of therapy may be clear. However, for the many patients with moderate-to-severe asthma who have more than 1 phenotype concurrently, such as allergic and eosinophilic asthma, or those meeting the prescribing criteria for multiple biologics ("multiply eligible"),[2] the optimal choice of biologic is uncertain.

All currently approved biologic therapies have been shown to improve asthma-related outcomes in individuals with asthma that is uncontrolled with conventional therapy. These include omalizumab, an anti-IgE that is approved for treatment of allergic asthma in individuals who have evidence of sensitivity to perennial allergens and IgE levels between 30 and 700 kU/L;

From [a]the Division of Allergy and Clinical Immunology, [b]the Channing Division of Network Medicine, and [g]the Division of General Internal Medicine, Brigham and Women's Hospital, Boston; [c]the Department of Epidemiology, [e]the Center for Drug Safety and Effectiveness, [i]the Department of Mental Health, and [j]the Department of Biostatistics, Johns Hopkins Bloomberg School of Public Health, Baltimore; [d]the Division of General Internal Medicine, Johns Hopkins University School of Medicine, Baltimore; [f]the Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston; and [h]the Division of Pediatric Allergy and Immunology, University of North Carolina, Chapel Hill.

Supported by the National Institutes of Health (NIH)/National Institute on Minority Health and Health Disparities (NIMHD) program K99/R00 MOSAIC (grant K99MD015767 [to A.T.A.]), a Brigham and Women's Hospital Minority Faculty Career Development Award (to A.T.A.), NIH/National Heart, Lung, and Blood Institute (NHLBI) (grant K23HL161332 [to D.F.]), the NIH/National Institute of Allergy and Infectious Diseases (NIAID) (grant K23AI163371 [to L.L.]), the NIH/NHLBI (grant K01HL145320 [to J.W.J.]), the NIH/National Institute on Aging (NIA) (K24AG049036 [to J.B.S.]).

Disclosure of potential conflict of interest: G. C. Alexander is past chair; in addition, he is a current member of the US Food and Drug Administration's Peripheral and Central Nervous System Advisory Committee and a cofounding principal and equity holder in Monument Analytics, a health care consultancy whose clients include the life sciences industry as well as plaintiffs in opioid litigation, and a past member of OptumRx's National Pharmacy and Therapeutics Committee. J. B. Segal has received unrelated grant funding from Bristol-Myers Squibb and has conducted unrelated consultancy for Sanofi and Provention Bio. The rest of the authors declare that they have no relevant conflicts of interest.

Received for publication September 15, 2022; revised January 9, 2023; accepted for publication January 13, 2023.

Available online February 3, 2023.

Corresponding author: Ayobami T. Akenroye, MBChB, MPH, PhD, Division of Allergy and Clinical Immunology, Brigham and Women's Hospital, 60 Fenwood Rd, Boston, MA 02115. E-mail: aakenroye@bwh.harvard.edu.

0091-6749

https://doi.org/10.1016/j.jaci.2023.01.020

Abbreviations used
ASMD: Absolute standardized mean difference
COVID-19: Coronavirus disease 2019
HR: Hazard ratio
ICD-9: *International Classification of Diseases, 9th revision*
ICD-10: *International Classification of Diseases, 10th revision*
IQR: Interquartile range
IRR: Incidence rate ratio
RPDR: Research Patient Data Registry

dupilumab, an anti–IL-4 receptor-α (anti–IL-4Rα) that has been shown to be effective in both allergic and eosinophilic asthma; and mepolizumab, an anti–IL-5 that is effective in individuals with eosinophilic asthma defined as having peripheral blood eosinophil counts of at least 150 cells/μL .[3,4]

In the absence of head-to-head trials, observational data can be used to emulate a hypothetical randomized trial, a target trial, to generate evidence about comparative effectiveness of medications and inform clinical decisions.[5-7] In the absence of head-to-head trials, this generates important evidence to inform clinical decisions. We conducted a retrospective cohort study that emulated a target trial to compare the effectiveness of omalizumab, dupilumab, and mepolizumab in reducing asthma-related exacerbations and improving lung function in individuals with asthma.

METHODS

Data source

We leveraged the integrated electronic health record from the Mass General Brigham Research Patient Data Registry (RPDR). The RPDR is a centralized clinical data registry of patient-related data from hospitals within the Mass General Brigham, the largest health care system in Massachusetts. This includes the Massachusetts General Hospital and the Brigham and Women's Hospital, which house the Mass General Brigham Asthma Center, specialized centers such as the Dana Farber Cancer Institute, and other affiliated hospitals such as the Faulkner Hospital. The RPDR currently holds clinical information on about 6 million patients since 1980. The information within the RPDR includes data from the electronic medical record systems; the billing systems; and the clinical data repository, which includes laboratory data and radiology results.[8] We conducted chart reviews to extract missing demographic and laboratory values, verify the indication for biologic use and that these individuals received the biologics indicated, and confirm comorbidities. This study was approved by the Mass General Brigham Institutional Review Board.

Study design and approach

The study design was based on target trial emulation, which is a cohort study design that uses design parameters similar to those of a hypothetical randomized control trial, including eligibility criteria, treatment arms and protocol, start of follow-up, and outcome assessment (see Table E1 in the Online Repository at www.jacionline.org).[5-7] Given that nonexperimental designs sometimes lead to biased estimates and spurious associations, explicit emulation of a target trial provides an opportunity to avoid common threats to validity from nonexperimental studies and/or identify how results from nonexperimental studies may be biased in comparison with the hypothetical randomized trial.

Study population

Patients aged 18 years or older with a diagnosis of moderate-to-severe asthma as identified by the *International Classification of Diseases, 9th revision* (ICD-9) or *International Classification of Diseases, 10th revision* (ICD-10) who received biologics between March 1, 2016, when mepolizumab was added to the institutional formulary, and August 31, 2021, and who did not have a concomitant code for other chronic lung diseases including cystic fibrosis, idiopathic pulmonary fibrosis, and chronic obstructive pulmonary disease were eligible for inclusion in the study. The index date was the date of initiation of the first biologic on or after March 1, 2016. However, we set the index date for dupilumab users as on or after November 1, 2018, when asthma was added to the institutional formulary as an indication for dupilumab following its approval for asthma in October 2018. We assumed that individuals who initiated dupilumab before this date had initiated therapy primarily for atopic dermatitis and thus were excluded from the analyses.

To avoid wrongfully attributing asthma as the indication for therapy, we also excluded individuals with ICD-9 or ICD-10 codes indicating other alternate indications for these biologics. Thus, we excluded individuals with ICD-9 or ICD-10 codes for chronic spontaneous urticaria, Churg-Strauss disease, hypereosinophilic syndrome, chronic sinusitis, nasal polyposis, and atopic dermatitis or those in whom dupilumab was prescribed by a dermatologist. Patients were followed from their index dates to 12 months later or August 31, 2021, whichever came first (see Fig E1 in the Online Repository at www.jacionline.org).

Reslizumab and benralizumab are rarely used in our center, leading to extremely small sample sizes, and tezepelumab had not been added to the institutional formulary at the time of this writing. Thus, they are not included in this study.

Study outcomes

The primary outcomes of interest were the cumulative incidence and incidence rate of clinically significant exacerbations (a composite of asthma exacerbation requiring steroids or hospitalization) over 12 months of follow-up. We included change in prebronchodilator FEV_1 value as a secondary outcome. Using previously validated methodology, we defined an exacerbation as an emergency room visit or a hospitalization event with a primary diagnostic code for asthma or an outpatient prescription for oral or intravenous corticosteroids.[9-11] Prescriptions for corticosteroids within 7 days of a prior prescription were considered to belong to the same exacerbation event. Asthma-related emergency room visits or hospitalizations were encounters with a primary code for asthma, wheezing, or bronchospasm that were spaced at least 7 days apart (see Table E2 in the Online Repository at www.jacionline.org).

Statistical analyses

Primary analyses were performed on the intention-to-treat population, which included all patients who initiated biologic therapy and met the study eligibility criteria regardless of subsequent switch to another biologic or discontinuation during the follow-up period. Categoric variables are reported as counts and percentages; continuous variables are reported as means and SDs for normally distributed data and as medians and interquartile ranges for skewed data.

Covariate adjustment

We leveraged 2 approaches to account for nonrandom allocation between the groups and emulate randomization at baseline. First, we focused on individuals for whom there was clinical equipoise: we restricted the study population to individuals with a serum IgE count between 30 and 700 IU/mL (the range of IgE levels used to determine eligibility for omalizumab) and an eosinophil count of at least 150 cells/μL (given mepolizumab and dupilumab's approval for use in eosinophilic asthma).[3,12] Thereafter, we used overlap weighting for each pairwise comparison including potential confounders between biologic use and exacerbation rates as identified in a directed acyclic graph constructed *a priori* (see Fig E2 in the Online Repository at www.jacionline.org). Overlap weighting outperforms inverse probability treatment weighting, in terms of bias and variance, for continuous, binary, and time-to-event outcomes.[13,14] It limits the occurrence of extreme weights; thus, its benefit increases as the degree of covariate overlap between groups decreases,

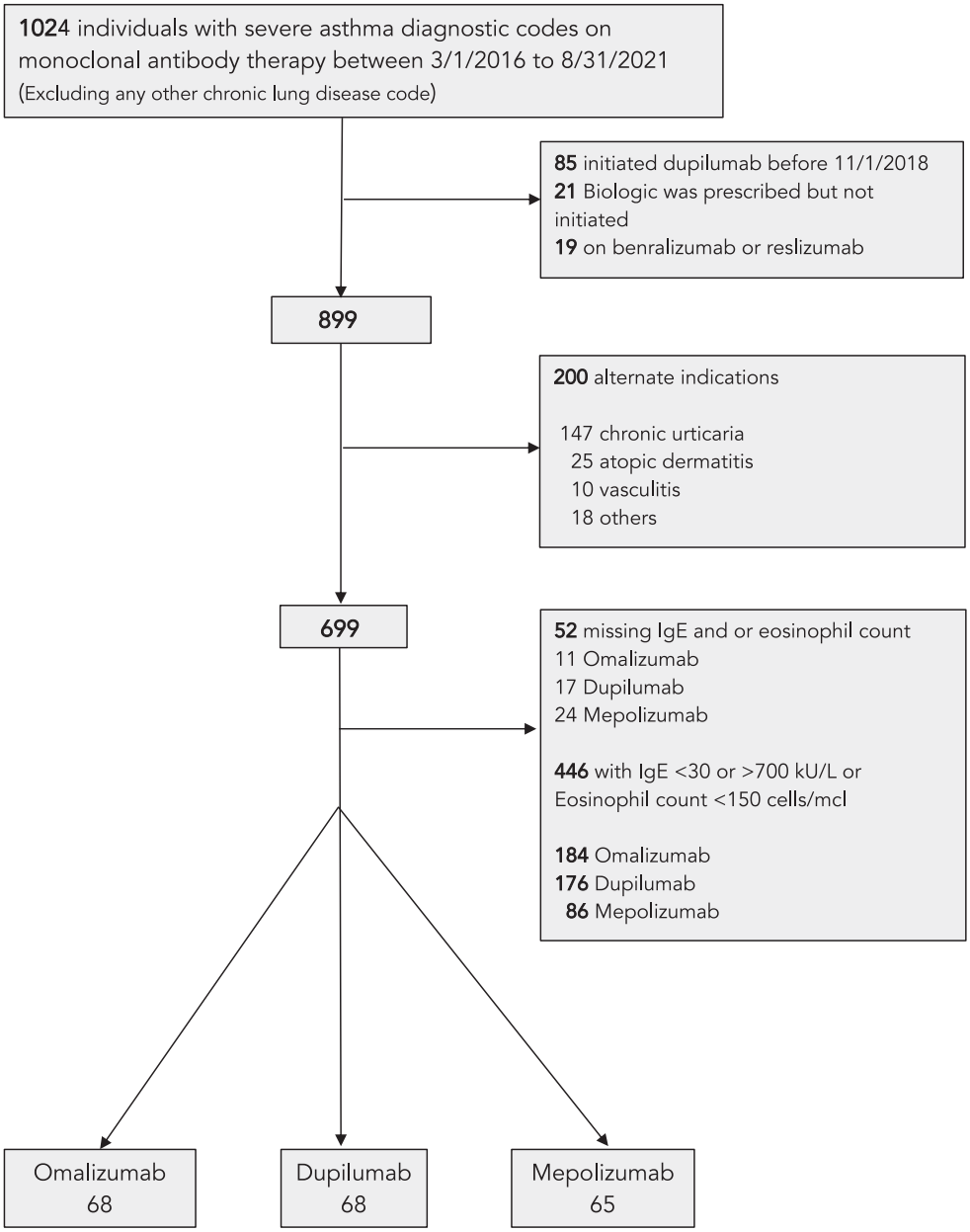

FIG 1. Flowchart showing selection of the study population.

and it is more robust to misspecification of the propensity score model.[14] On a related note, it has been shown to weight to an overlap population between groups being compared while balancing measured covariates.[15] The variables used for weighting included age, sex, race/ethnicity, insurance, baseline asthma control using the annualized exacerbation rate preindex date, preindex eosinophil count, preindex IgE level, baseline FEV_1 value, use of an inhaled corticosteroid or long-acting β-agonist, body mass index, smoking status, presence of allergic rhinitis, Charlson comorbidity index, season of biologic initiation, and patient's residence in the inner core. The inner core was as defined by the Metropolitan Area Planning Council in Massachusetts.[16] We evaluated covariate balance by plotting the absolute standardized mean differences (ASMDs).[17] An ASMD of 0.10 or less was considered acceptable.[18,19]

We used overlap-weighted negative binomial regression models to calculate incidence rate ratios (IRRs) for the exacerbations; we fit an overlap-weighted Cox proportional-hazards model and plotted cumulative incidence risk curves for time to first exacerbation. We used a mixed-effects repeated-measures model to evaluate the changes in prebronchodilator FEV_1 value from baseline to week 52. This model was adjusted for the aforementioned covariates along with the baseline FEV_1 value, time, and interaction terms for time with treatment group and time with baseline FEV_1 value. We also evaluated outcomes in patients within this cohort with an eosinophil count of at least 300 cells/μL, which is a clinically significant threshold. All analyses were performed with R statistical software, version 3.6.0 (R Foundation for Statistical Computing, Vienna, Austria).[20]

Sensitivity analyses

We conducted several sensitivity analyses to evaluate the robustness of our results and explore the possibility of spurious inferences due to residual confounding. First, our study period extended to periods following the onset of the coronavirus disease 2019 (COVID-19) pandemic, which may have influenced asthma admissions and/or emergency department utilization. Therefore, we tested the outcomes when limiting the sample to those who initiated biologic therapy on or before October 1, 2019, to allow a minimum of

TABLE I. Baseline characteristics of the study population

	Omalizumab	Mepolizumab	Dupilumab*
Overall sample size, no.	68	65	68
Age (y), mean, SD	47.7 (16.2)	54.5 (13.6)	51.7 (13.9)
Female sex, no. (%)	54 (79.4%)	43 (66.2%)	42 (61.8%)
Body mass index (kg/m^2), mean (SD)	30.1 (7.8)	29.2 (7.5)	28.3 (6.6)
Race			
White, no. (%)	52 (76.5%)	49 (75.4%)	54 (79.4%)
Black, no. (%)	3 (4.4%)	9 (13.8%)	4 (5.9%)
Asian, no. (%)	2 (2.9%)	0 (0.0%)	4 (5.9%)
Ethnicity			
Hispanic, no. (%)	2 (2.9%)	2 (3.1%)	1 (1.5%)
Residence in inner city, no. (%)	11 (16.2%)	8 (12.3%)	13 (19.1%)
Private insurance†	48 (70.6%)	47 (72.3%)	55 (80.9%)
Concomitant medication(s)			
ICS/LABA, no. (%)	35 (51.5%)	39 (60.0%)	42 (61.8%)
LAMA, no. (%)	17 (25.0%)	24 (36.9%)	14 (20.6%)
OCS, no. (%)	4 (5.9%)	4 (6.2%)	2 (2.9%)
Baseline eosinophil count (cells/μL), median (IQR)	305 (190-472)	630 (400-1010)	410 (278-642)
Baseline IgE level (IU/mL), median (IQR)	144 (80-276)	120 (65-295)	166 (74-285)
Preindex annualized exacerbation rate (%), mean (SD)	0.8 (1.6)	1.1 (1.4)	0.8 (1.2)
Prebronchodilator FEV_1 value (L), median (IQR)	2.1 (1.7-2.7)	2.2 (1.7-2.8)	2.0 (1.5-2.6)
Prebronchodilator FEV_1 percent predicted (%), median (IQR)	83 (69-92)	72 (62-83)	81 (69-93)
Charlson comorbidity index, mean (SD)	1.2 (0.8)	1.3 (0.7)	1.1 (1.1)
Smoking status			
Current, no. (%)	2 (2.9%)	3 (4.6%)	5 (7.4%)
Former, no. (%)	13 (19.1%)	9 (13.8%)	15 (22.1%)
Never, no. (%)	44 (64.7%)	41 (63.1%)	37 (54.4%)
Unknown, no. (%)	9 (13.2%)	12 (18.5%)	11 (16.2%)
Allergic rhinitis, no. (%)	63 (92.6%)‡	48 (73.8%)	55 (80.9%)
Season of initiation			
Winter, no. (%)	9 (13.2%)	13 (20.0%)	26 (38.2%)

ICS/LABA, Inhaled corticosteroid/long-acting β-agonist; *LAMA*, long-acting muscarinic antagonist; *OCS*, oral corticosteroid.
*Of the 68 patients taking dupilumab, 66 (97%) were using the dose of 300 mg every 2 weeks.
†No patient within this cohort was uninsured.
‡The 5 patients who initiated omalizumab but who were categorized as not having allergic rhinitis all had IgE levels within the accepted range for omalizumab dosing and a documented history of perennial rhinitis. However, we did not see the objective evidence of testing to perennial allergens.

TABLE II. IRR of exacerbations

	IRR (95% CI)		
Drug	Mepolizumab	Omalizumab	Dupilumab
Mepolizumab (reference)	1.00	0.78 (0.32-1.91)	0.28 (0.09-0.84)
Omalizumab (reference)		1.00	0.36 (0.12-1.08)
Dupilumab (reference)			1.00

6 months of follow-up through March 1, 2020. Second, we evaluated emergency room visits for nonasthma conditions in the 1-year follow-up period as a negative outcome control, expecting no difference between groups. Third, we included a switch to another biologic as a failure event in the time-to-event analyses.[21]

RESULTS

Study population

A total of 201 adult patients met the inclusion criteria (Fig 1). This included 68 individuals who began taking dupilumab, 68 who began taking omalizumab, and 65 who began taking mepolizumab (Table I). All measured covariates were well balanced following overlap weighting with an ASMD less than 0.10 (see Fig E3 in the Online Repository at www.jacionline.org).

Comparison of incidence rates of exacerbations

The median duration of follow-up was 1.6 years for dupilumab (interquartile range [IQR] = 1.2-2.0), 3.1 years for omalizumab (IQR = 1.9-4.2), and 3.0 years for mepolizumab (IQR = 1.9-4.1). Over 12 months of follow-up, 31 exacerbations occurred over 68 person years (0.46 exacerbations per person ear) in the dupilumab group, 63 over 68 person years (0.93 exacerbations per person year) in the omalizumab group, and 86 over 65 person years (1.32 exacerbations per person year) in the mepolizumab group (the adjusted IRR for dupilumab vs mepolizumab was 0.28 [95% CI = 0.09-0.84], the IRR for dupilumab vs omalizumab was 0.36 [95% CI = 0.12-1.08], and the IRR for omalizumab vs mepolizumab was 0.78 [95% CI = 0.32-1.91]) (Table II). In patients with an eosinophil count of at least 300 cells/μL, the

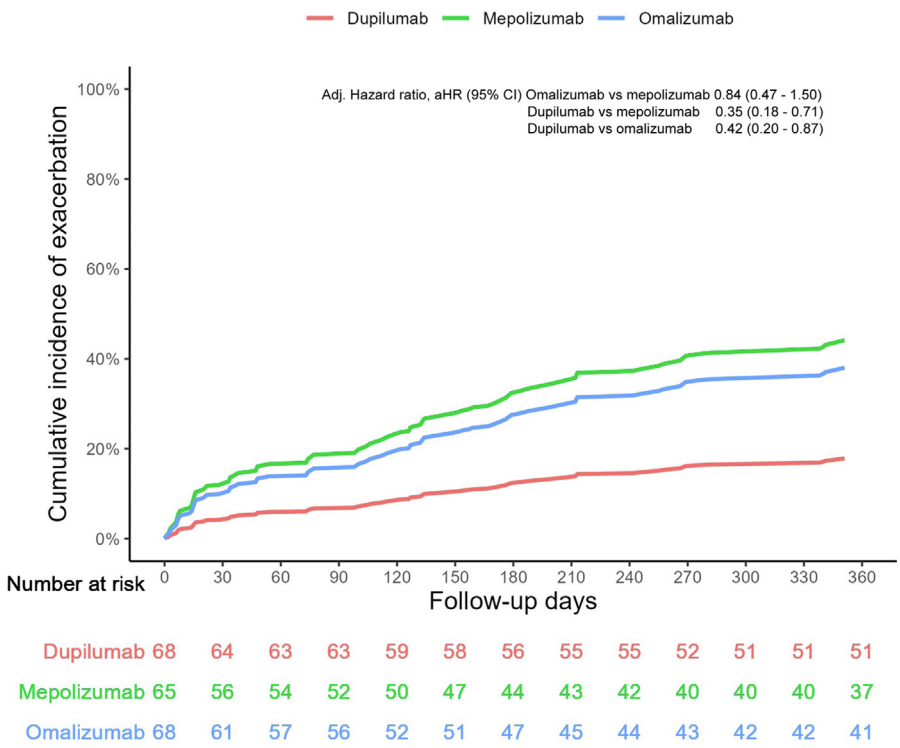

FIG 2. Cumulative incidence of exacerbations over 12 months of follow-up.

IRR comparing dupilumab with mepolizumab was 0.26 (95% CI = 0.08-0.82) and the IRR comparing dupilumab with omalizumab was 0.33 (95% CI = 0.09-1.24) (see Table E3 in the Online Repository at www.jacionline.org).

Comparison of cumulative incidence of exacerbations

Over 12 months of follow-up, asthma-related exacerbations occurred in 17 patients (25.0%) in the dupilumab group, 28 (43.1%) in the mepolizumab group, and 27 (39.7%) in the omalizumab group (the adjusted hazard ratios [HRs] were as follows: for dupilumab vs mepolizumab, 0.35 [95% CI= 0.18-0.71]; for dupilumab vs omalizumab, 0.42 [95% CI = 0.20-0.87]; and for omalizumab vs mepolizumab, 0.84 [95% CI 0.47-1.50]) (Fig 2). In patients with eosinophil counts of at least 300 cells/μL, the HR comparing dupilumab with mepolizumab was 0.26 (95% CI = 0.10-0.67) and the HR for dupilumab vs omalizumab was 0.24 (95% CI = 0.09-0.63) (see Fig E4 in the Online Repository at www.jacionline.org).

Counting switch to another biologic as a failure event

In all, 11 patients (18.6%) taking omalizumab, 1 patient (1.4%) taking dupilumab, and 16 patients (25.0%) taking mepolizumab switched therapy during the period of follow-up. In analyses including switch to other biologics as a failure event, the HR comparing dupilumab with mepolizumab was 0.44 (95% CI = 0.28-0.71), the HR comparing dupilumab with omalizumab was 0.72 (95% CI = 0.43-1.21), and the HR comparing omalizumab with mepolizumab was 0.62 (95% CI = 0.38-1.00) (Fig 3).

Change from baseline in prebronchodilator FEV_1 value

At 12 months of follow-up, the change from baseline in the prebronchodilator FEV_1 value was greater in patients receiving dupilumab than in those receiving mepolizumab (mean difference = 0.110 L [95% CI = –0.003 to 0.222 L (P = .056)]) or omalizumab (mean difference = 0.082 L [95% CI = –0.040 to 0.204 L (P = .118)]). However, these changes were not statistically significant (Table III). The results in the subgroup with eosinophil counts of at least 300 cells/μL were consistent (see Table E4 in the Online Repository at www.jacionline.org).

Sensitivity analyses and negative outcome

Of the 68 individuals taking dupilumab, 51 (75.0%) had initiated therapy on or before October 1, 2019, as did 62 (95.4%) of the 65 patients taking mepolizumab, and 61 (89.7%) of the 68 patients taking omalizumab. The HR for exacerbations in those taking dupilumab versus in those taking mepolizumab was 0.25 (95% CI = 0.11-0.59); the HR for exacerbations in those taking dupilumab versus in those taking omalizumab was 0.22 (95% CI = 0.09-0.54); and the HR for exacerbations in those taking omalizumab versus in those taking mepolizumab, was 1.12 (95% CI = 0.63-2.01) (see Fig E5 in the Online Repository at www.jacionline.org). The HRs of emergency room visits for non-asthma conditions in the 1-year period after baseline were not significantly different between the groups (see Fig E6 in the Online Repository at www.jacionline.org).

DISCUSSION

Despite the essential role that biologics play in the treatment of moderate-to-severe asthma, little is known regarding the real-

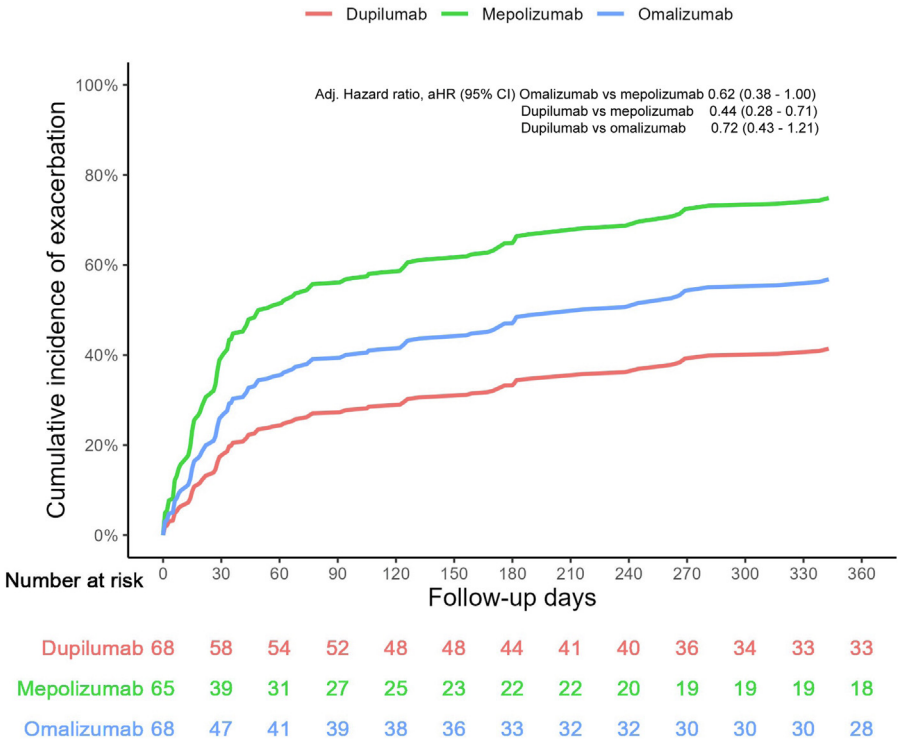

FIG 3. Cumulative incidence of exacerbations over 12 months of follow-up, including switch as a failure event.

TABLE III. Change from baseline to 1 year in prebronchodilator FEV_1 value

	Mean difference in liters (95% CI)		
Drug	**Mepolizumab**	**Omalizumab**	**Dupilumab**
Mepolizumab (reference)	0	0.028 (–0.083 to 0.140)	0.110 (–0.003 to 0.222)
Omalizumab (reference)		0	0.082 (–0.040 to 0.204)
Dupilumab (reference)			0

world comparative effectiveness of these products. Given the costs of these products[22] and the fact that individuals with severe asthma bear a disproportionate burden of asthma-related morbidity and mortality, the opportunity costs for choosing a less effective biologic in an individual with severe asthma are significant and delay could be fatal.[23,24] In this retrospective cohort study using electronic health records data from a large health care system, we found that dupilumab was associated with a lower hazard of asthma-related exacerbations than were omalizumab or mepolizumab in individuals with IgE levels between 30 and 700 kU/L (the range of IgE for which omalizumab is approved) and eosinophil counts of at least 150 cells/μL. In addition, we found that patients being treated with dupilumab had greater improvements in FEV_1 value than did patients in the mepolizumab and omalizumab groups. However, the differences in FEV_1 value were not statistically significant. The results were similar in the subgroup of patients with an eosinophil count of at least 300 cells/μL. Our conclusions remained unchanged in multiple sensitivity analyses.

Our findings extend those from 2 recent indirect treatment comparisons showing that dupilumab may be more effective than omalizumab and mepolizumab in decreasing asthma-related exacerbations and improving lung function.[25,26] However, in those studies (which used aggregate-level data from published randomized placebo-controlled trials), the differences between these therapies did not meet clinically important thresholds.[26-29] In this study using individual-level data from a health care system, we found reductions by half or greater in the risk of exacerbations when dupilumab was compared with mepolizumab and omalizumab. For FEV_1 value, the mean difference in improvement in FEV_1 value comparing dupilumab with mepolizumab in these patients with eosinophilic or allergic asthma was more than 100 mL, although the 95% CI crossed the null value of 0. Currently, however, there are no validated clinically important differences for reduction of exacerbation rates and FEV_1 value in asthma and these differences need to be evaluated in other clinical cohorts.[30] Additionally, differences between the populations recruited into those randomized placebo-controlled trials and our clinic population may account for these differences.[31] For instance, the mean exacerbation rate in the year before initiation of a biologic in this study was 1 compared with 2 in the dupilumab trials and more than 3 in the seminal mepolizumab trials.[26] Furthermore, we limited our study cohort by IgE level and eosinophil count. However, in the seminal randomized trials of dupilumab, the

baseline eosinophil count was higher than in the mepolizumab trials, and two-thirds of patients in the dupilumab trials were reported as having allergic rhinitis. These facts may potentially influence response to these therapies, accounting for some of the differences between those indirect comparisons and this study.[29] Although indirect comparisons can be useful when evidence from head-to-head trials is unavailable, the results may be limited by differences in the study populations of the therapies being compared and by the unavailability of individual patient data.[32] Moreover, the results of indirect comparisons may still differ from results of studies of clinic populations given that many of these trials had strict inclusion and exclusion criteria. For instance, obese patients were less likely to have been recruited into these asthma trials of biologics in individuals with asthma.[31] Nonetheless, taken altogether, the evidence to date suggests that dupilumab may be more clinically effective than mepolizumab and omalizumab in improving exacerbations and lung function.

The greater effectiveness of dupilumab may be related to its mechanism of action. Dupilumab is a broad-spectrum "type 2" biologic. It blocks both IL-4 and IL-13 signaling, thereby decreasing B-cell class switch to IgE.[33] In addition, it prevents differentiation of naive T_H cells to T_H2 cells, thus decreasing canonical T_H2 cytokines such as IL-5– and IL-5–induced eosinophil recruitment, the mechanism deployed by the anti–IL-5, mepolizumab.[3,34] By blocking IL-13, dupilumab may also affect the airway hyperreactivity, goblet cell hyperplasia, and smooth muscle dysfunction associated with asthma, and it may account for dupilumab's remarkable effect in improving prebronchodilator FEV_1 value.[35]

The strengths of this study include the use of data from an integrated health system, which provides the opportunity to capture clinical variables and laboratory data (including eosinophil count), which are important when comparing these biologics, and to capture outcomes including exacerbations and lung function. Although the patients prescribed each biologic may be different, this data source provided the opportunity to balance important covariates across biologic groups. Using an innovative nonexperimental design, we addressed a question of interest with important clinical relevance to the management of patients with moderate-to-severe asthma for which there is little to no evidence to date. Furthermore, we used real-world data, which may be more reflective of how these biologics perform in a usual care setting rather than in a monitored trial setting.

Our study also has limitations. First, we had a relatively small sample size, and power in detecting differences may have been limited, especially in comparisons of omalizumab and mepolizumab. Furthermore, as with any observational study, the subgroups of patients using these medications differed at baseline, and there is a risk of residual confounding. Additionally, there may be temporal trends in asthma outcomes, care, or assessment over calendar time. However, we tried to mitigate these concerns by emulating a hypothetical trial and adjusting for measured confounders. We were able to achieve covariate balance using propensity score weighting of overlap weights. Our results were generally robust to multiple sensitivity analyses and demonstrate biologic plausibility given our current understanding of type 2 inflammation. Furthermore, analyses limited to the pre–COVID-19 pandemic era also provided similar conclusions. Secondly, although real-world data may be more representative than trial populations, our study population is small and drawn from a single health care system in the northeastern region of the United States. Only approximately 10% to 15% of the individuals identified as belonging to underrepresented minority groups, and fewer than 30% of them were publicly insured. Furthermore, we excluded children, those with concomitant comorbidities, and those restricted by baseline eosinophil count and IgE level. Thus, our results may be limited in generalizability to pediatric populations with asthma, those with comorbidities, and/or those with IgE level and eosinophil count outside the ranges used in this study. Thus, additional work is needed to generate evidence in more diverse and representative populations. Third, patients may have been prescribed a biologic but did not use it, and adherence to background asthma therapy while taking biologics may be associated with improved outcomes of treatment with these biologics. However, we included patients with 2 or more prescriptions for the index biologic and included baseline use of maintenance inhaled corticosteroid or long-acting β-agonist in the statistical models. Finally, we have not considered safety events, although the optimal choice of biologic includes a delicate balance between safety and effectiveness. Although dupilumab was most effective, there is emerging evidence on additional safety events associated with dupilumab, with a recent labeling change to include arthralgias and avoidance of live vaccines.[36] Thus, more research on dupilumab's long-term safety is needed.

In summary, this study using data from a single integrated health care system suggests that dupilumab has the lowest overall risk of asthma-related exacerbations when compared with omalizumab and mepolizumab in individuals with an eosinophil count of at least 150 cells/μL and an IgE level between 30 and 700 kU/L. These data add to indirect comparisons of clinical trials to suggest that dupilumab may be a better choice for multiply eligible patients. Additional research including multiply eligible individuals or individuals who meet criteria for both eosinophilic and allergic asthma is needed to generate evidence about whether there is a hierarchy of phenotypes in these individuals—that is, whether the allergic phenotype should be targeted before the eosinophilic phenotype in these individuals or vice versa. Such a hierarchy would have important implications for the stepwise approach to initiation of mAb in asthma treatment.

Key messages

- **In this clinical cohort of patients with eosinophil counts of at least 150 cells/μL and IgE levels of 30 to 700 kU/L.**
- **Dupilumab was associated with greater reductions in exacerbations than mepolizumab and omalizumab.**
- **Dupilumab was associated with greater than 100-mL improvement in FEV_1 value compared with mepolizumab, but this did not meet the statistical significance threshold.**

REFERENCES

1. Drazen JM, Harrington D. New biologics for asthma. N Engl J Med 2018;378:2533-4.
2. Akenroye A, McCormack M, Keet C. Severe asthma in the US population and eligibility for monoclonal antibody therapy. J Allergy Clin Immunol 2020;145:1295-7.e6.
3. Brusselle GG, Koppelman GH. Biologic therapies for severe asthma. N Engl J Med 2022;386:157-71.
4. Fajt ML, Wenzel SE. Asthma phenotypes and the use of biologic medications in asthma and allergic disease: the next steps toward personalized care. J Allergy Clin Immunol 2015;135:299-310, quiz 1.

5. Hernan MA, Sauer BC, Hernandez-Diaz S, Platt R, Shrier I. Specifying a target trial prevents immortal time bias and other self-inflicted injuries in observational analyses. J Clin Epidemiol 2016;79:70-5.
6. Hernan MA, Robins JM. Using big data to emulate a target trial when a randomized trial is not available. Am J Epidemiol 2016;183:758-64.
7. Hernán MA. Methods of public health research - strengthening causal inference from observational data. N Engl J Med 2021;385:1345-8.
8. Liao KP, Cai T, Savova GK, Murphy SN, Karlson EW, Ananthakrishnan AN, et al. Development of phenotype algorithms using electronic medical records and incorporating natural language processing. BMJ 2015;350:h1885.
9. Foer D, Beeler PE, Cui J, Karlson EW, Bates DW, Cahill KN. Asthma exacerbations in patients with type 2 diabetes and asthma on glucagon-like peptide-1 receptor agonists. Am J Respir Crit Care Med 2021;203:831-40.
10. Lane SJ, Petersen H, Seltzer JM, Blanchette CM, Navaratnam P, Allen-Ramey F, et al. Moderate symptom-based exacerbations as predictors of severe claims-based exacerbations in asthma. JAMA 2013;50:642-8.
11. Fuhlbrigge A, Peden D, Apter AJ, Boushey HA, Camargo CA Jr, Gern J, et al. Asthma outcomes: exacerbations. J Allergy Clin Immunol 2012;129(suppl 3): S34-48.
12. Xolair prescribing information 2021. Updated 07/2021. Available at: https://www.gene.com/download/pdf/xolair_prescribing.pdf. Accessed April 8, 2022.
13. Cheng C, Li F, Thomas LE. Addressing extreme propensity scores in estimating counterfactual survival functions via the overlap weights. Am J Epidemiol 2022;191: 1140-51.
14. Zhou Y, Matsouaka RA, Thomas L. Propensity score weighting under limited overlap and model misspecification. Stat Methods Med Res 2020;29:3721-56.
15. Thomas LE, Li F, Pencina MJ. Overlap Weighting: A propensity score method that mimics attributes of a randomized clinical trial. JAMA 2020;323:2417-8.
16. Metropolitan Area Planning Council (MAPC): Massachusetts community types 2021. Available at: https://www.mapc.org/get-involved/subregions/icc/#comm. Accessed April 8, 2022.
17. Zhang Z, Kim HJ, Lonjon G, Zhu Y, written on behalf of AMEB- DCTCG. Balance diagnostics after propensity score matching. Ann Transl Med 2019;7:16.
18. Harder VS, Stuart EA, Anthony JC. Propensity score techniques and the assessment of measured covariate balance to test causal associations in psychological research. Psychol Methods 2010;15:234-49.
19. Stuart EA, Lee BK, Leacy FP. Prognostic score-based balance measures can be a useful diagnostic for propensity score methods in comparative effectiveness research. J Clin Epidemiol 2013;66(suppl 8):S84-90.e1.
20. Team RC. R: A language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing; 2019.
21. Lieberman JA, Stroup TS, McEvoy JP, Swartz MS, Rosenheck RA, Perkins DO, et al. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. N Engl J Med 2005;353:1209-23.
22. Mauger D, Apter AJ. Indirect treatment comparisons and biologics. J Allergy Clin Immunol 2019;143:84-6.
23. Nurmagambetov T, Kuwahara R, Garbe P. The economic burden of asthma in the United States, 2008-2013. Ann Am Thorac Soc 2018;15:348-56.
24. The Global Asthma Report 2018. Global Asthma Network. Available at: http://globalasthmareport.org/2018/index.html. Accessed January 28, 2022.
25. Bateman ED, Khan AH, Xu Y, Guyot P, Chao J, Kamat S, et al. Pairwise indirect treatment comparison of dupilumab versus other biologics in patients with uncontrolled persistent asthma. Respir Med 2022;191:105991.
26. Akenroye A, Lassiter G, Jackson JW, Keet C, Segal J, Alexander GC, et al. Comparative efficacy of mepolizumab, benralizumab, and dupilumab in eosinophilic asthma: a bayesian network meta-analysis. J Allergy Clin Immunol 2022; 150:1097-105.e12.
27. Agache I, Rocha C, Beltran J, Song Y, Posso M, Solà I, et al. Efficacy and safety of treatment with biologicals (benralizumab, dupilumab and omalizumab) for severe allergic asthma: a systematic review for the EAACI Guidelines - recommendations on the use of biologicals in severe asthma. Allergy 2020;75: 1043-57.
28. 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.
29. Nopsopon T, Lassiter G, Chen ML, Alexander GC, Keet C, Hong H, et al. Comparative efficacy of tezepelumab to mepolizumab, benralizumab, and dupilumab in eosinophilic asthma: a Bayesian network meta-analysis [e-pub ahead of print]. J Allergy Clin Immunol https://doi.org/10.1016/j.jaci.2022.11.02. Accessed December 17, 2022.
30. Bonini M, Di Paolo M, Bagnasco D, Baiardini I, Braido F, Caminati M, et al. Minimal clinically important difference for asthma endpoints: an expert consensus report. Eur Respir Rev 2020;29:190137.
31. Akenroye A, Keet C. Underrepresentation of blacks, smokers, and obese patients in studies of monoclonal antibodies for asthma. J Allergy Clin Immunol Pract 2020;8: 739-41.e6.
32. Salanti G, Higgins JP, Ades AE, Ioannidis JP. Evaluation of networks of randomized trials. Stat Methods Med Res 2008;17:279-301.
33. Pelaia G, Vatrella A, Maselli R. The potential of biologics for the treatment of asthma. Nat Rev Drug Discov 2012;11:958-72.
34. Israel E, Reddel HK. Severe and difficult-to-treat asthma in adults. N Engl J Med 2017;377:965-76.
35. Manuyakorn W, Howarth PH, Holgate ST. Airway remodelling in asthma and novel therapy. Asian Pac J Allergy Immunol 2013;31:3-10.
36. Dupixent [dupilumab] FDA Labels, Warnings, Reactions: FDA Report; 2022. Available at: https://fda.report/SrLC/1709. Accessed May 16, 2022.