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Mepolizumab real-world effectiveness in severe asthma with an eosinophilic phenotype and overlapping severe allergic asthma

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ABSTRACT

Background: Some patients with severe asthma have overlapping allergic and eosinophilic phenotypes and may be eligible for anti-eosinophilic or anti-immunoglobin E (IgE) biologics.
Objective: This post hoc sub-analysis assessed real-world mepolizumab effectiveness in patients with overlapping allergic and eosinophilic phenotypes, using 1-year data from the international, prospective REALITI-A (REAL world effectiveness of mepolizumab In paTIent care – Asthma) study.
Methods: The clinically significant asthma exacerbations (CSE) rate was assessed 1 year before (pretreatment) and after (follow-up) mepolizumab treatment, stratified by baseline total IgE (tIgE) levels (<60, 60 to <190, 190 to <550, and ≥550 kilounits per litre [kU/L]), atopic status (yes/no/unknown), previous omalizumab use (yes/no), geographic baseline omalizumab eligibility (eligible/non-eligible), and baseline tIgE level and blood eosinophil count threshold combinations (<81 or ≥81 kU/L and <300 or ≥300 cells per microliter [cells/μL]).
Results: Overall, 822 patients were included. CSEs occurred in 760 patients (93%) pretreatment and 398 patients (49%) during follow-up. CSE rate (rate ratio [95% CI]) was reduced in follow-up across all tIgE subgroups (<60 [n = 173]: 0.31 [0.25-0.37]; 60 to <190 [n = 176]: 0.30 [0.25-0.36]; 190 to <550 [n = 170]: 0.26 [0.20-0.33]; ≥550 kU/L [n = 155]: 0.28 [0.23-0.35]) and irrespective of atopic status (yes [n = 422]: 0.29 [0.26-0.33]; no [n = 52]: 0.33 [0.23-0.47]; unknown [n = 348]: 0.28 [0.24-0.32]), previous omalizumab use (yes [n = 151]: 0.37 [0.30-0.45]; no [n = 671]: 0.27 [0.24-0.30]), or eligibility (eligible [n = 349]: 0.29 [0.25-0.34]; non-eligible [n = 191]: 0.32 [0.27-0.38]). Furthermore, the CSE rate was reduced across all tIgE (kU/L) and blood eosinophil count (cells/μL) combinations (<81/<300 [n = 53]: 0.34 [0.24-0.47]; <81/≥300 [n = 103]: 0.33 [0.26-0.41]; ≥81/<300 [n = 98]: 0.36 [0.28-0.47]; ≥81/≥300 [n = 249]: 0.26 [0.22-0.31]).
Conclusion: Mepolizumab demonstrates real-world effectiveness in reducing exacerbations in patients with severe asthma and an eosinophilic phenotype, regardless of any overlapping allergic phenotype.

Disclaimer: All authors had full access to the data on request and had final responsibility for the decision to submit for publication.
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Introduction

Severe asthma is a complex, heterogeneous disease of the airways involving distinct but interrelated immune-inflammatory pathways.[1,2] The advancements in severe asthma classifications have stemmed from studies identifying commonalities in clinical (phenotype) and/or biological (endotype) characteristics of the disease.[3-5] The main asthma classifications identified from these studies are generally stratified by the presence or absence of an allergic or eosinophilic phenotype.[3-5] Allergic asthma is characterized by symptoms caused by exposure to seasonal and/or perennial aeroallergens and elevated allergen-specific immunoglobin E (IgE) levels, with eligibility for anti-IgE agents if the patient is sensitized to clinically relevant perennial aeroallergens.[2,6] In contrast, patients with eosinophilic asthma can be defined as those with elevated sputum or blood eosinophil counts (BECs) irrespective of etiology.[1,2,6]

Although a number of biologics are now available for the treatment of severe asthma, there is only 1 biologic specifically approved for patients with severe asthma with an allergic phenotype (omalizumab), whereas a number are approved specifically for those with an eosinophilic phenotype (mepolizumab, reslizumab, and benralizumab).[2] The separation of allergic and eosinophilic phenotypes in severe asthma is reflected in clinical treatment guidelines, in which distinct biologic treatment recommendations are provided for patients depending on the perceived phenotype.[1,7,8] However, this delineation may be too simplistic as real-world evidence suggests that up to half of patients with asthma have overlapping phenotypes often associated with both allergic and eosinophilic classifications.[9] Moreover, a post hoc analysis of 4 clinical trials determined that more than three-quarters of patients with moderate-to-severe eosinophilic asthma also met the study's criteria for allergic asthma (positive skin prick test result and/or allergen-specific serum IgE levels of >0.35 kilounits per litre [kU/L]).[6] Similarly, a post hoc analysis of the observational cross-sectional IDEAL (The Identification and Description of sEvere Asthma patients in a cross-sectionaL study) (NCT02293265) study highlighted the overlap in omalizumab and mepolizumab treatment eligibility in patients with severe asthma, with up to 73% of patients having dual eligibility for mepolizumab and omalizumab, depending on the eligibility criteria used.[10] In such situations, multiple biologic treatment options may be available; thus, there is a need to better understand the impact of these therapies in this overlapping phenotype patient population.

Mepolizumab is a humanized monoclonal antibody that targets interleukin (IL)-5, the primary cytokine involved in the proliferation, activation, and survival of eosinophils.[11] Mepolizumab is approved worldwide as an add-on therapy for severe asthma with an eosinophilic phenotype,[12-14] and the benefit of mepolizumab treatment in these patients has been demonstrated across several clinical trials and real-world studies, notably the international, prospective REALITI-A (REAL world effectiveness of mepolizumab In paTIent care – Asthma) study.[15-27] A meta-analysis of the MENSA (Mepolizumab as Adjunctive Therapy in Patients with Severe Asthma) (NCT01691521) and MUSCA (Mepolizumab adjUnctive therapy in subjects with Severe eosinophiliC Asthma) (NCT02281318) randomized controlled studies highlighted the benefit of mepolizumab in a patient population with overlapping allergic and eosinophilic severe asthma, with reduced rates of clinically significant exacerbations found with mepolizumab irrespective of previous omalizumab use, total IgE levels, or atopic phenotype.[28] PREDICTUMAB (Predictive Factors and Magnitude of Response to Omalizumab and Mepolizumab in Allergic and Eosinophilic Severe Asthma: a Pragmatic Multicenter Trial in Belgium), a clinical study performing head-to-head comparisons of the efficacy of omalizumab and mepolizumab in patients eligible for both drugs is ongoing and expected to complete at the end of 2024.[29] However, equivalent real-world evidence is required to help clinicians determine the optimal treatment for patients with an overlapping phenotype who may be eligible for more than 1 biologic, per guideline recommendations.[1,7,8]

Here, we performed a post hoc subanalysis of data from the REALITI-A study at 1 year to assess the real-world impact of mepolizumab, prescribed in clinical care for severe asthma, in patients who have or do not have an overlapping severe allergic asthma phenotype, to understand the impact of this overlapping phenotype on the response to mepolizumab. In this analysis, we have stratified exacerbation outcomes by baseline total IgE levels, previous omalizumab use, omalizumab eligibility status, atopic status, or baseline total IgE levels in combination with baseline BEC. Omalizumab was the longest-standing and most prescribed biologic specific for severe allergic asthma and therefore considered the most appropriate biologic comparison for these analyses.

Methods

Study Design

REALITI-A (GSK ID: 204710) was a 24-month international, prospective, single-arm, observational cohort study enrolling patients with asthma who were newly prescribed mepolizumab treatment by their physician; the study details have been reported previously,[26] and the study design is outlined in Figure 1. Briefly, patients were enrolled between December 2016 and October 2019 and the index date was defined as the time that the first dose of mepolizumab (100 mg subcutaneous) was administered. REALITI-A included a planned 1-year intermediary cutoff. This post hoc subanalysis used data from patients who participated in the full 24-month study period, comparing results 1 year before starting treatment (pretreatment) with data 12 months after mepolizumab treatment (1-year follow-up period). Pretreatment data were collected retrospectively, and follow-up data were collected contemporaneously at routine asthma health care visits.

Patients

Patients were eligible for enrollment if they met the following key criteria: (1) more than or equal to 18 years of age, (2) had a current clinical diagnosis of asthma, (3) had a physician decision to initiate mepolizumab treatment, and (4) had relevant medical records for more than or equal to 12 months before enrollment. Patients were excluded if they had received mepolizumab treatment in the 12 months before enrollment; however, previous use of other biologic medications was permitted. Patients who had participated in an interventional clinical trial within the 12 months before enrollment were also excluded. This study was conducted in accordance with the Declaration of Helsinki as revised in 2013; local ethical approval was obtained per study site. Written informed consent was obtained from each patient before commencing any study-related activities.

End Points and Assessments

The objectives for the REALITI-A study have been described previously; the primary end point was the rate of clinically significant asthma exacerbations (CSEs) during the pretreatment and follow-up periods.[26] This post hoc analysis assessed the rate of CSEs during the pretreatment and follow-up periods stratified by the following: (1) baseline total IgE levels, (2) previous omalizumab use, (3) current omalizumab eligibility based on European Union (EU)/Japan criteria, (4) atopic status, and (5) baseline total IgE level and BEC threshold combinations. CSEs were defined as deterioration in asthma control requiring use of systemic corticosteroids (SCS) and/or emergency department visit and/or hospitalization. Use of SCS was defined as oral corticosteroids (OCS) for more than or equal to 3 days or a single

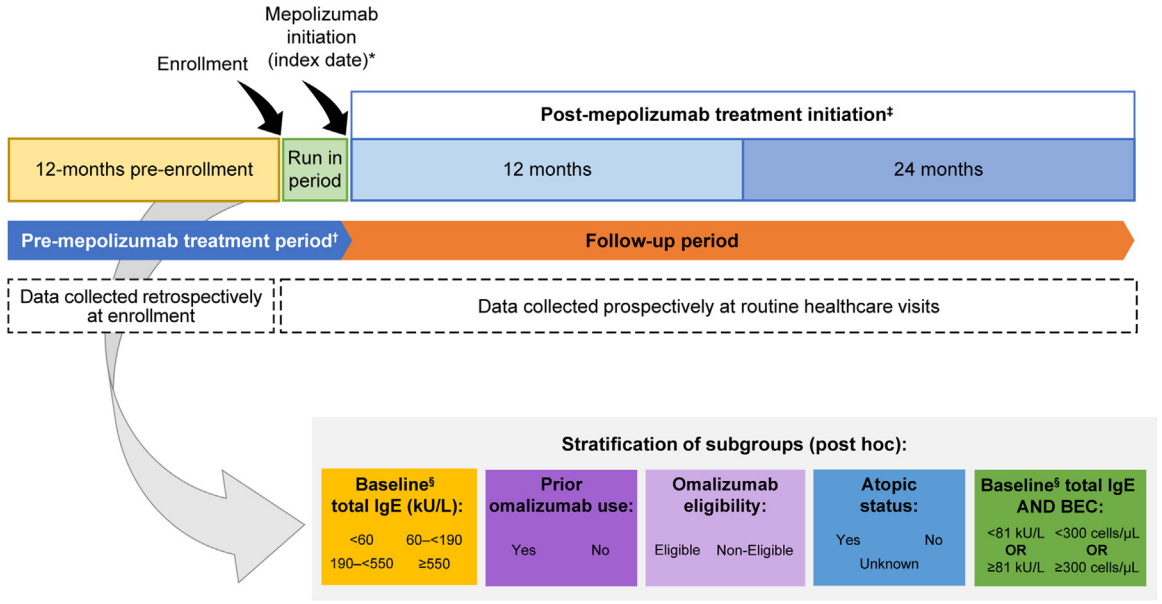

Figure 1. Study design. *The index date is the date that the first dose of mepolizumab (100 mg subcutaneous) was administered; †the pretreatment period consisted of the 12 months before enrollment plus a variable-length run-in period; ‡this post hoc analysis assessed the listed subgroups using interim data from the full study population at 1 year for patients enrolled between December 2016 and October 2019; §baseline is at mepolizumab initiation or the most recent value available within 90 days before mepolizumab initiation. BEC, blood eosinophilic count; cells/μL, cells per microliter; IgE, immunoglobin E; kU/L, kilounits per litre.

systemic administration (intravenous/intramuscular) of SCS due to worsening of asthma symptoms. A patient was defined as "atopic" if they had a positive skin prick test result or any specific allergen IgE level more than 0.35 international units per milliliter (IU/mL) (for continuous readings; >0 for categorical readings). If a patient had either a negative skin prick test result or all-specific allergen IgE level ≤0.35 IU/mL (or both), their status was recorded as "not atopic". A patient with no specific allergen test and no skin prick test results available was recorded as having "unknown" atopic status. Omalizumab eligibility following EU/Japan criteria was defined as a positive skin prick test result or radioallergosorbent test score for at least 1 of 5 aeroallergens (house dust mite, dog dander, cat dander, *Alternaria*, and cockroach) and a specified body weight (kilograms) and pretreatment total IgE (IU/mL) combination (20-50 kg and 30-1500 IU/mL, >50 to 60 kg and 30-1200 IU/mL, >60 to 70 kg and 30-1000 IU/mL, >70 to 80 kg and 30-900 IU/mL, >80-90 kg and 30-800 IU/mL, >90 to 125 kg and 30-600 IU/mL, and >125 to 150 kg and 30-500 IU/mL).[13,14]

Statistical Analysis

The rate of CSEs was analyzed using a generalized estimating equation model assuming a negative binomial distribution with pretreatment and 12-month follow-up time periods as a covariate. The variance of the estimated mean was corrected for within-patient correlation, and the logarithm of time was included as an offset variable. For the likelihood of no exacerbations, data were modeled using a logistic regression model comparing the pretreatment and follow-up periods using a generalized estimating equation model, with a covariate of treatment period (pretreatment and follow-up). The pretreatment period consisted of the 365 days before enrollment into the study and is inclusive of any period between study enrollment and the index date. The follow-up period included up to 52 weeks after the index date and was reported per patient until the earliest of death, study withdrawal, the end of the follow-up period, switch to another biologic, or off-label dose of mepolizumab. Subgroup analyses were performed by quartile divisions of baseline total IgE level (<60, 60 to <190, 190 to <550, and ≥550 kU/L), previous omalizumab use (yes/no), omalizumab eligibility (eligible/non-eligible), atopic status (yes/no/unknown), and baseline total IgE level and BEC standard threshold combinations[30-32] (<81 kU/L or ≥81 kU/L and <300 cells/μL or ≥300 cells per microliter [cells/μL]).

Results

Patient Population

In total, 822 patients were treated with mepolizumab. Most (n = 654 [80%]) were still receiving mepolizumab treatment at the end of the follow-up period, whereas 147 (18%) had discontinued. The primary reasons for treatment discontinuation were lack of efficacy (n = 47 [6%]), patient decision (n = 34 [4%]), switch to another biologic (n = 25 [3%]), adverse event (n = 17 [2%]), investigator discretion (n = 8 [<1%]), and others (n = 16 [2%]). There were 21 patients who reached the conclusion of the study without a record of whether they had discontinued mepolizumab.

Demographics and Characteristics

The patient baseline demographics and characteristics have been described previously[26] and are found in Table 1 stratified by baseline total IgE levels, previous omalizumab use, baseline omalizumab eligibility, atopic status, and baseline total IgE levels in combination with baseline BEC. Overall, 674 patients had available baseline total IgE data, and the number of patients in each baseline total IgE subgroup was generally similar (<60 kU/L, n = 173; 60 to <190 kU/L, n = 176; 190 to <550 kU/L, n = 170; ≥550 kU/L, n = 155). Of the 822 patients with available data on previous omalizumab use, 151 (18%) had previously used omalizumab, with a mean (SD) treatment period of 33.6 (35.3) months. The main reason for omalizumab discontinuation was lack of efficacy, as reported by 119 patients (79%). Sufficient information to assess omalizumab eligibility was available for 540 patients; of these, 349 (65%) were eligible for omalizumab treatment. Of all 822 patients, 422 were identified as atopic, 214 as nonatopic, and 186 had an unknown atopic status. In total, 504 patients had available data on both baseline total IgE in combination with BEC.

Baseline demographics and characteristics were generally similar between the treated population and the subgroups analyzed (Table 1),

Table 1
Patient Demographics and Clinical Characteristics at Enrollment

Demographic/ characteristic	Treated population (N = 822)	Baseline total IgE (N = 674)				Previous omalizumab use (N = 822)		Omalizumab eligibility (N = 540)		Atopic status (N = 822)			Baseline total IgE (kU/L)/blood eosinophil count (cells/μL) combinations (N = 504)			
		<60 kU/L (n = 173)	60-<190 kU/L (n = 176)	190-<550 kU/L (n = 170)	≥550 kU/L (n = 155)	Yes (n = 151)	No (n = 671)	Eligible (n = 349)	Non-eligible (n = 191)	Yes (n = 422)	No (n = 214)	Unknown (n = 186)	<81/<300 (n = 53)	<81/≥300 (n = 103)	≥81/<300 (n = 99)	≥81/≥300 (n = 249)
Age, mean (SD), y	54.0 (13.6)	54.3 (13.4)	53.4 (13.5)	53.7 (13.2)	53.2 (15.1)	51.5 (15.0)	54.6 (13.2)	52.3 (14.3)	53.9 (14.3)	52.3 (14.6)	56.0 (12.6)	55.8 (11.9)	59.8 (12.0)	52.0 (13.4)	53.5 (15.5)	53.5 (13.2)
Female, n (%)	521 (63)	142 (82)	108 (61)	99 (58)	69 (45)	97 (64)	424 (63)	220 (63)	119 (62)	259 (61)	138 (64)	124 (67)	42 (79)	84 (82)	49 (49)	140 (56)
Age at asthma onset, mean (SD), y	34.5 (19.4)	33.4 (18.5)	33.9 (19.2)	35.4 (18.3)	34.5 (21.55)	32.1 (20.0)	35.0 (19.2)	32.5 (19.6)	34.6 (20.1)	32.2 (19.8)	37.4 (18.4)	36.3 (18.9)	37.5 (20.3)	33.7 (16.9)	32.8 (22.3)	34.6 (18.79)
Asthma duration,	n = 801	n = 172	n = 174	n = 163	n = 146	n = 146	n = 655	n = 341	n = 185	n = 412	n = 212	n = 177	n = 53	n = 103	n = 94	n = 244
mean (SD), y	19.7 (15.7)	20.6 (16.6)	19.5 (15.2)	18.9 (15.4)	18.4 (15.5)	19.4 (15.0)	19.7 (15.9)	19.8 (15.5)	19.5 (15.6)	20.1 (15.5)	18.7 (16.0)	19.8 (15.7)	22.7 (18.7)	17.9 (14.5)	20.7 (15.9)	19.3 (15.7)
Patients with maintenance OCS use, n (%)	319 (39)	64 (20)	66 (21)	77 (24)	54 (17)	60 (19)	259 (81)	132 (41)	80 (25)	157 (37)	96 (45)	67 (36)	20 (38)	40 (39)	51 (52)	90 (36)
Maintenance OCS dose,[a]	n = 298	n = 59	n = 62	n = 71	n = 53	n = 58	n = 240	n = 125	n = 76	n = 148	n = 90	n = 59	n = 16	n = 39	n = 46	n = 85
mg/d, median (Q1, Q3)	10 (5.0, 14.7)	10 (6.0, 20.0)	10 (5.0, 15.0)	7.5 (5.0, 14.7)	10 (5.0, 10.7)	10 (6.3, 20.0)	10 (5.0, 12.7)	10 (5.0, 15.0)	10 (5.0, 14.7)	10 (5.0, 12.5)	8 (5.0, 12.5)	10 (6.4, 20.0)	10 (6.5, 17.5)	10 (5.0, 10.8)	10 (5.0 16.5)	5.7 (5.0, 11.4)
Smoking history, n (%)	n = 815	n = 171	n = 174	n = 170	n = 153	n = 151	n = 664	n = 346	n = 188	n = 419	n = 212	n = 185	n = 52	n = 102	n = 98	n = 249
Never	489 (60)	112 (65)	100 (57)	100 (59)	81 (53)	90 (60)	399 (60)	209 (60)	113 (60)	264 (63)	128 (60)	111 (60)	38 (73)	61 (60)	58 (59)	139 (56)
Current	25 (3)	8 (5)	5 (3)	5 (3)	6 (4)	3 (2)	22 (3)	7 (2)	9 (5)	9 (2)	6 (3)	8 (4)	3 (6)	3 (3)	3 (3)	6 (2)
Former	301 (37)	51 (30)	69 (40)	65 (38)	66 (43)	58 (38)	243 (37)	130 (38)	66 (35)	146 (35)	78 (37)	66 (36)	11 (21)	38 (37)	37 (38)	104 (42)
Blood eosinophil count,	n = 614	n = 131	n = 131	n = 134	n = 107	n = 114	n = 500	n = 257	n = 135	n = 313	n = 165	n = 136	n = 53	n = 103	n = 99	n = 249
cells/μL,[b] geometric mean (SD log)	353 (1.24)	319 (1.08)	340 (1.31)	412 (1.36)	365 (1.05)	357 (1.25)	353 (1.24)	352 (1.23)	303 (1.28)	350 (1.26)	380 (1.18)	310 (1.33)	100 (1.11)	590 (0.52)	80 (1.28)	670 (0.58)
Previous omalizumab use n (%)	150 (18)	11 (6)	33 (19)	47 (28)	38 (25)	150 (>99)[c]	0	150 (43)	0	113 (27)	13 (6)	26 (14)	2 (4)	7 (7)	26 (26)	67 (26)
Treatment duration, mean (SD), mo	33.6 (35.3)	21.5 (25.9)	29.3 (31.2)	32.6 (31.5)	32.3 (34.3)	33.6 (35.3)	–	33.6 (35.3)	–	32.1 (33.4)	47.0 (27.9)	33.2 (45.5)	39.0 (46.7)	23.1 (26.1)	40.3 (45.6)	29.6 (25.4)
Total IgE, geometric mean	n = 674	n = 173	n = 176	n = 170	n = 155	n = 130	n = 544	n = 327	n = 186	n = 379	n = 177	n = 119	n = 53	n = 103	n = 99	n = 249
(SD log), kU/L[b]	181.3 (1.63)	22.6 (0.98)	110.3 (0.33)	324.2 (0.30)	1251.0 (0.73)	289.6 (1.15)	148.1 (1.65)	213.2 (1.08)	131.4 (2.48)	249.3 (1.49)	81.0 (1.53)	144.4 (1.59)	24.3 (0.80)	28.8 (1.07)	362.5 (0.97)	368.0 (1.02)

Abbreviations: cells/μL, cells per microliter; IgE, immunoglobin E; kU/L, kilounits per litre; m, months; NA, not available; OCS, oral corticosteroid; Q1, first quartile; Q3, third quartile; y, years.
[a]Defined as the average daily dose in milligram expressed as prednisone equivalent in the 28 days before index.
[b]The most recent value in the 90 days before mepolizumab initiation.
[c]One patient had a record of omalizumab in concomitant medications but answered "no" to previous use.

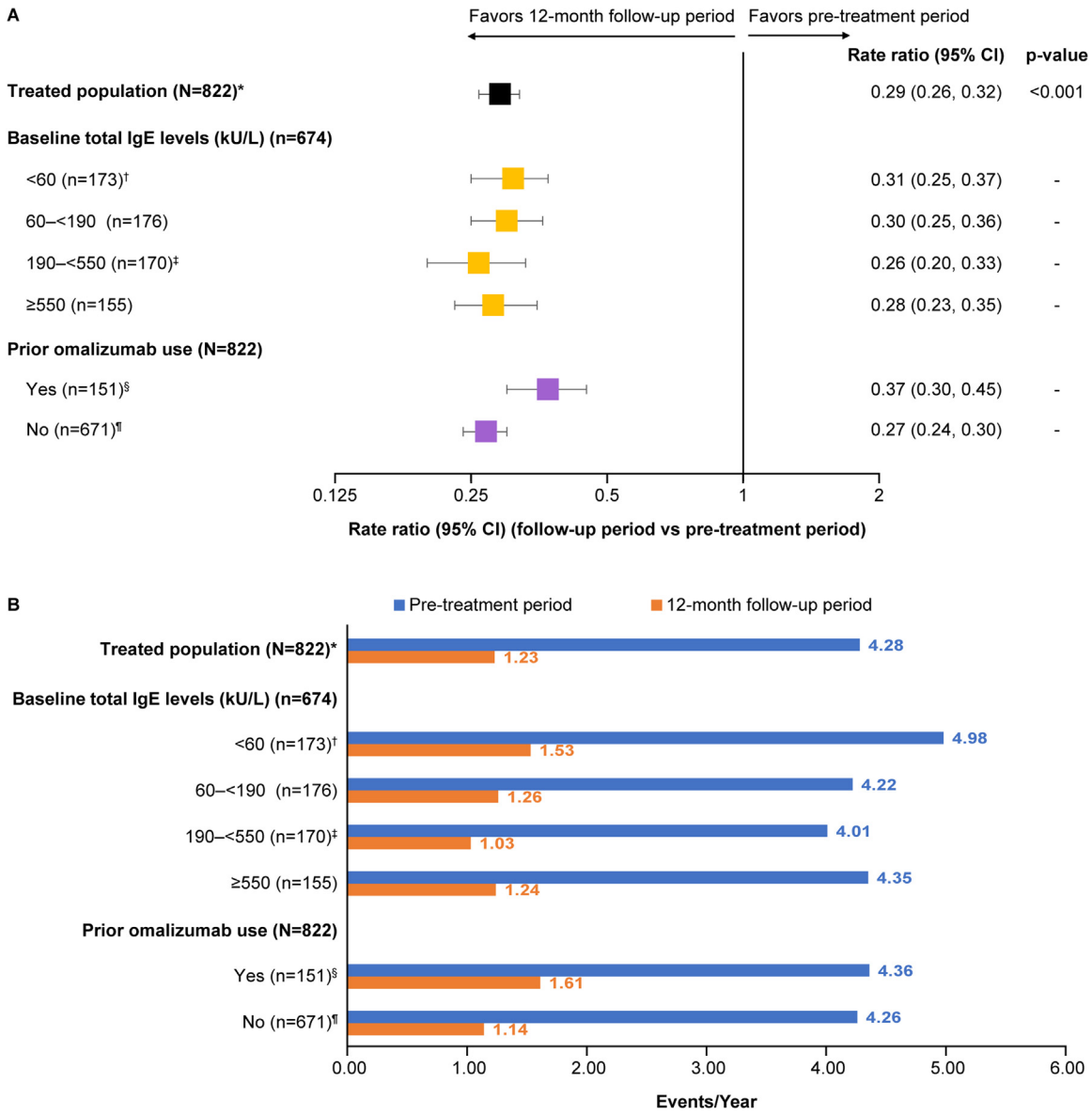

Figure 2. Rate of CSEs (A) and CSE events per year (B) between the pretreatment and 12-month follow-up periods according to baseline total IgE levels and previous omalizumab use. The pretreatment period consisted of the 365 days before enrollment into the study and is inclusive of any period between study enrollment and initiating mepolizumab treatment. Baseline was at mepolizumab initiation or the most recent value available within 90 days before mepolizumab initiation. The follow-up period included up to 52 weeks after mepolizumab treatment initiation and was reported per patient until the earliest of death, study withdrawal, the end of the follow-up period, switch to another biologic, or off-label dose of mepolizumab. *For the pretreatment period and follow-up periods, n = 821 and n = 820, respectively; †for the follow-up period, n = 171; ‡for the pretreatment period, n = 169; §for the pretreatment period, n = 150; ¶for the follow-up period, n = 669. CSE, clinically significant exacerbations; IgE, immunoglobin E; kU/L, kilounits per litre.

with differences of note described in subsequent texts. Across the baseline total IgE subgroups, the less than 60 kU/L subgroup had the highest proportion of females, longest mean asthma duration, and fewer patients who had previous omalizumab use compared with the other total IgE subgroups. Patients in the 190 to less than 550 kU/L baseline total IgE subgroup had the highest baseline BEC. Non-atopic patients had slightly shorter mean asthma duration, lower baseline total IgE levels, but slightly higher mean age at asthma onset and baseline BECs compared with their atopic (or unknown) counterparts. When looking at patients stratified by baseline total IgE levels and BEC combinations, patients with total IgE level less than 81 kU/L had the highest proportion of females, regardless of BEC. Patients with baseline total IgE level less than 81 kU/L and BEC less than 300 cells/μL had the longest mean asthma duration. More patients with baseline total IgE levels more than or equal to 81 kU/L had previous omalizumab use compared with the lower total IgE subgroups, regardless of BEC. In the total IgE levels more than or equal to 81 kU/L subgroups, patients with BEC less than 300 cells/μL received maintenance OCS use in the highest proportion. Patients with previous omalizumab use had a higher baseline total IgE level compared with those with no previous omalizumab use. When stratified by omalizumab eligibility status, patients eligible for omalizumab had a higher baseline BEC and total IgE level compared with patients who were non-eligible for omalizumab treatment.

Rates of Clinically Significant Exacerbations

CSEs occurred in 760 patients (93%) during the pretreatment period and in 398 patients (49%) during the follow-up period. Mepolizumab significantly reduced the rate of CSEs in follow-up vs the pretreatment period (rate ratio [RR]: 0.29, 95% CI: 0.26-0.32; $P < .001$). The rate of CSEs was reduced irrespective of baseline total IgE levels or previous omalizumab use (Fig 2A); a numerically greater

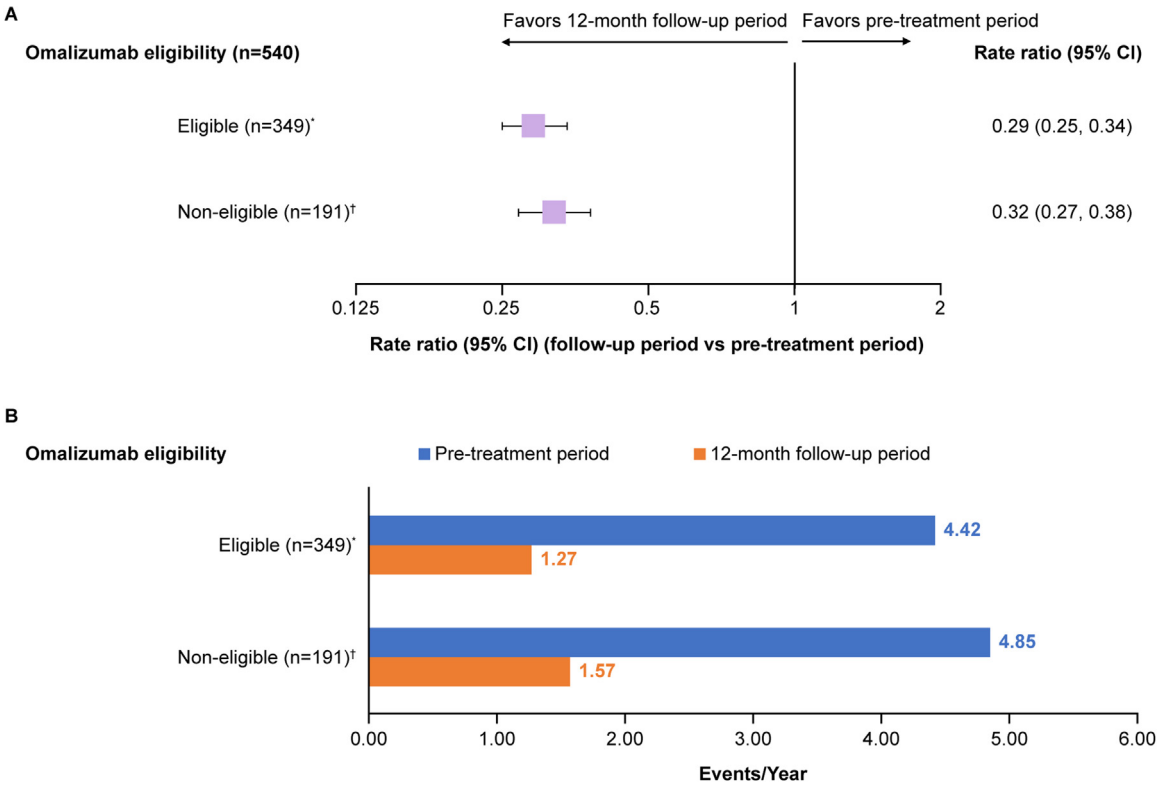

Figure 3. Rate of CSEs (A) and CSE events per year (B) between the pretreatment and 12-month follow-up periods according to omalizumab eligibility. The pretreatment period consisted of the 365 days before enrollment into the study and is inclusive of any period between study enrollment and initiating mepolizumab treatment. Baseline was at mepolizumab initiation or the most recent value available within 90 days before mepolizumab initiation. The follow-up period included up to 52 weeks after mepolizumab treatment initiation and was reported per patient until the earliest of death, study withdrawal, the end of the follow-up period, switch to another biologic, or off-label dose of mepolizumab. *For the pretreatment and follow-up period, n = 348; †for the follow-up period, n = 190. CSE, clinically significant exacerbations.

reduction from pretreatment to follow-up in the rate of CSEs was observed in patients with no previous omalizumab treatment (73%; RR: 0.27, 95% CI: 0.24-0.30) than in those with previous omalizumab treatment (63%; RR: 0.37, 95% CI: 0.30-0.45).

Similarly, irrespective of omalizumab eligibility, the rate of CSEs was reduced during the 12-month follow-up period vs the pretreatment period (Fig 3A). The rate of CSEs was also reduced during the 12-month follow-up period vs the pretreatment period regardless of atopic status, with similar reductions observed in patients with atopic status (71%; RR: 0.29, 95% CI: 0.26-0.33), non-atopic status (71%; RR: 0.29, 95% CI: 0.24-0.34), and unknown status (71%; RR: 0.29, 95% CI: 0.23-0.35) (Fig 4A). When comparing combinations of baseline total IgE levels and BEC thresholds, the rate of CSEs was also reduced during the 12-month follow-up period vs the pretreatment period across all combinations (Fig 5A). Patients with baseline total IgE levels more than or equal to 81 kU/L and a BEC more than or equal to 300 cells/μL had a slightly greater reduction in the rate of CSEs (74%; RR: 0.26, 95% CI: 0.22-0.31) than the other combinations (64%-67%; RR: 0.33-0.36, 95% CI: 0.24-0.28 to 0.41-0.47). The number of CSE events per year in the 12-month follow-up versus pretreatment period are also reported by baseline total IgE levels and prior omalziumab use (Fig. 2B), omalizumab eligibility (Fig. 3B), atopic status (Fig. 4B) and baseline total IgE and BEC threshold combinations (Fig. 5B).

Discussion

Many patients with severe asthma who require biologic therapy may be eligible for more than 1 biologic due to overlapping phenotypes, such as allergic and eosinophilic asthma. This post hoc analysis, using data from the REALITI-A full study population at 1 year, assessed whether a co-existent allergic phenotype in patients with severe eosinophilic asthma influenced the effectiveness of mepolizumab in reducing CSEs. The analysis revealed that real-world mepolizumab treatment significantly reduced the rate of CSEs in patients with severe asthma who exhibit both eosinophilic and allergic “atopic” phenotypes. These data suggest that addressing eosinophilic disease by inhibiting IL-5 with mepolizumab[33] results in improved outcomes irrespective of allergic phenotype.

Baseline demographics and characteristics were generally similar across the subgroups analyzed and treated population. Of note, the highest proportion of maintenance OCS use (52%) was among patients with total IgE levels of more than or equal to 81 kU/L and BECs of less than 300 cells/μL. These results are not totally unexpected, as maintenance OCS use is associated with a reduction in BECs.[34,35] However, previous omalizumab treatment was third highest among these patients across all subgroups (27%). Together, this is potentially indicative of increased likelihood of severe uncontrolled asthma in this particular subgroup.[8]

In this analysis, the rate of CSEs was reduced by 63% to 74% irrespective of baseline total IgE levels or previous omalizumab use. These data expand on the findings from the meta-analysis of the MENSA and MUSCA studies, which revealed the benefit of mepolizumab in an overlapping phenotype patient population.[28] In addition, these data are consistent with the results from the open-label OSMO study (NCT02654145) and associated post hoc analysis, which reported a 64% reduction in CSEs in patients with severe eosinophilic asthma who were switched to mepolizumab after suboptimal asthma control with omalizumab treatment.[16,36] Although subgroups were not statistically compared and there was variability in subgroup sample sizes, our analysis reported a slightly smaller reduction in the rate of CSEs in patients who had

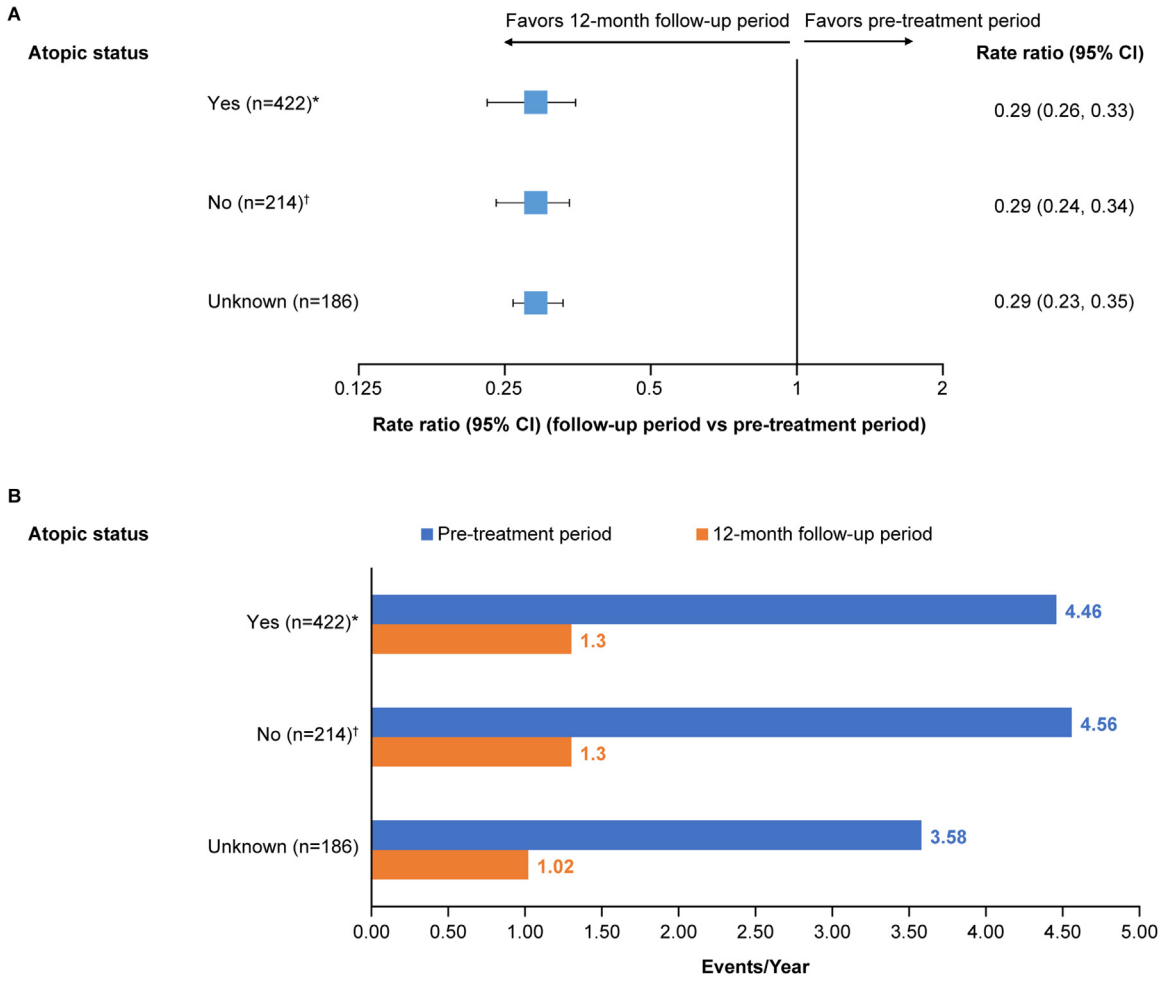

Figure 4. Rate of CSEs (A) and CSE events per year (B) between the pretreatment and 12-month follow-up periods according to atopic status. The pretreatment period consisted of the 365 days before enrollment into the study and is inclusive of any period between study enrollment and initiating mepolizumab treatment. Baseline was at mepolizumab initiation or the most recent value available within 90 days before mepolizumab initiation. The follow-up period included up to 52 weeks after mepolizumab treatment initiation and was reported per patient until the earliest of death, study withdrawal, the end of the follow-up period, switch to another biologic, or off-label dose of mepolizumab. *For the pretreatment and follow-up periods, n = 421; †for the follow-up period, n = 213. CSE, clinically significant exacerbations.

previous omalizumab use than those who had not. This was not attributable to any difference in baseline BEC on entry into the REALITI-A study. Thus, although omalizumab treatment can reduce BECs[37] and mepolizumab efficacy has been found to correlate with BEC,[19,20,38] the lesser reduction in the rate of CSEs observed in patients with previous omalizumab use in this study cannot be attributed to lower BECs in these patients. Perhaps more probable is that despite having evidence of type 2 inflammation, these patients had more complex disease, explaining their inadequate response to omalizumab. Eosinophilic inflammation can be driven by both allergic and non-allergic factors, and, in more complex disease, non-type 2 neutrophilic airway inflammation may also be present along with type 2 airway inflammation. This is not apparent from peripheral blood measures and only disclosed by induced sputum analysis.[39] Induced sputum was not evaluated in REALITI-A, but it has been found that the co-existence of neutrophilic airway inflammation may modify the response to type 2-directed biologic therapy, which may help explain the observations in our analysis.[39] Nonetheless, mepolizumab was effective in reducing exacerbations irrespective of previous omalizumab use.

This analysis reports that the rate of CSEs was reduced by 68% to 71% regardless of omalizumab eligibility status. Notably, in this study, 57% of patients who were eligible for omalizumab treatment had no previous omalizumab use, despite Global Initiative for Asthma 2023 and European Respiratory Society/American Thoracic Society 2014 guidelines recommending omalizumab for patients meeting similar eligibility criteria to those used in this analysis.[7,8] This may be a reflection of biologic use in general, as there is evidence that eligible patients might not receive biologics, including omalizumab, from primary care- or office-based respiratory consultants.[40,41] This potentially indicates a lack of awareness and/or adherence to treatment guidelines among some physicians,[8,42] and therefore, the familiarization of physicians with biologic therapies is essential to the full realization of their therapeutic potential.[42,43] In addition, aside from specialist access, other factors, such as age, race/ethnicity, annual household income, insurance type, and geographic jurisdictions, have been found to influence access to biologics in patients with asthma, which may explain any discrepancies between biologic eligibility and utilization observed.[44] The findings from this study highlight the real-world benefit of mepolizumab in patients with severe asthma with an overlapping allergic and eosinophilic phenotype. As such, the data support the use of mepolizumab as a treatment option in these patients, a consideration not currently reflected in treatment guidelines.[1,7,8]

Mepolizumab treatment also resulted in 71% reductions in the rate of CSEs irrespective of atopic status. These results build on a previously reported post hoc analysis of the randomized phase III clinical trial, MENSA, in which mepolizumab-treated patients with severe asthma also experienced reductions in CSEs irrespective of atopic status or house dust mite sensitivity.[45]

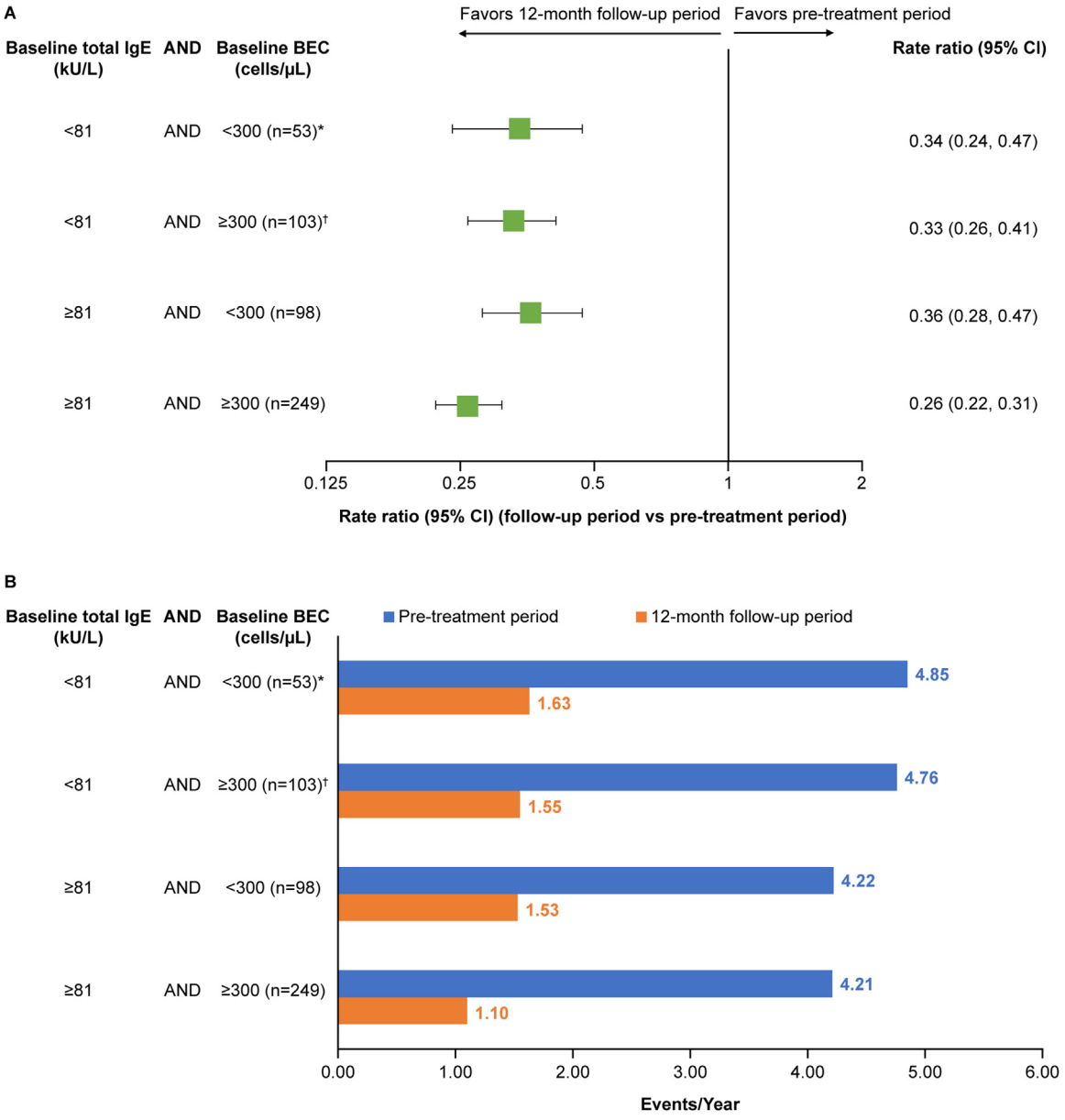

Figure 5. Rate of CSEs (A) and CSE events per year (B) between the pretreatment and 12-month follow-up periods according to baseline total IgE level and BEC threshold combinations. The pretreatment period consisted of the 365 days before enrollment into the study and is inclusive of any period between study enrollment and initiating mepolizumab treatment. Baseline was at mepolizumab initiation or the most recent value available within 90 days before mepolizumab initiation. The follow-up period included up to 52 weeks after mepolizumab treatment initiation and was reported per patient until the earliest of death, study withdrawal, the end of the follow-up period, switch to another biologic, or off-label dose of mepolizumab. *For the follow-up period, n = 52; †for the follow-up period, n = 102. BEC, blood eosinophil count; cells/μL, cells per microliter; CSE, clinically significant exacerbations; IgE, immunoglobin E; kU/L, kilounits per litre.

After mepolizumab treatment, a reduction in the rate of CSEs was also observed across all combinations of baseline total IgE levels and BECs assessed, with the greatest reduction in patients with the highest total IgE threshold and BEC combination (≥81 kU/L and ≥300 cells/μL). This is in line with findings from a post hoc analysis of data from the Dose Ranging Efficacy And safety with Mepolizumab in severe asthma (DREAM) (NCT01000506) and MENSA clinical trials, which revealed mepolizumab had the greatest efficacy in patients with the highest BECs (≥500 cells/μL).[38] However, in previous analyses from the REALITI-A and REal worlD Effectiveness and Safety of Mepolizumab in a Multicentric Spanish Cohort of Asthma Patients Stratified by Eosinophils (REDES) studies, patients with eosinophilic asthma had improved outcomes with mepolizumab treatment, irrespective of baseline BECs,[23,27] and several studies found that baseline BEC was not predictive of super-response or remission after treatment with anti-IL-5 biologics.[39,46,47]

The limitations of the REALITI-A study have been published previously, including its single-arm and open-label design, resulting in a lack of comparator for unblinded mepolizumab treatment; although, the open-label data capture is typical for real-world assessments.[26] The limitations of this analysis include its post hoc nature, which led to suboptimal patient group sizes for the previous omalizumab use subgroups. Moreover, most patients (>80%) included in the analysis did not have previous omalizumab use. It should be appreciated that this analysis is not a comparison of omalizumab vs mepolizumab in severe asthma. The previous history of omalizumab use has been used as an indicator of omalizumab eligibility and the comparison of outcomes in those who have or have not previously been prescribed omalizumab. Furthermore, it is not an attempt to reveal that mepolizumab works in omalizumab failures, which has previously been found in the OSMO study.[36] The assessment of omalizumab eligibility was based on the broader EU/Japan eligibility criteria, in

comparison to the more restrictive US eligibility criteria.[48] However, using the EU/Japan eligibility criteria does not account for regional specific registration policies for omalizumab treatment.[49] It is also worth noting that if omalizumab discontinuation had occurred less than 4 half-lives (half-life: 26 days) before enrollment, this may have influenced baseline assessments such as those of IgE or BEC levels.[48] In addition, when defining atopic and non-atopic statuses, a positive allergen-specific IgE or skin prick test result may not mean that the aeroallergen assessed is necessarily inducing asthma symptoms. However, we also analyzed omalizumab eligibility which is a step beyond purely severe asthma with a positive atopic status, which may have introduced some selection bias for the classification of patients as having atopic asthma.

In conclusion, these data reveal the real-world benefit of mepolizumab treatment in patients with overlapping allergic and eosinophilic severe asthma by reducing CSEs irrespective of baseline total IgE levels, previous omalizumab use, omalizumab eligibility, atopic status, and baseline total IgE level and BEC threshold combinations. Overall, these findings should provide confidence that patients with severe asthma who have an overlapping allergic and eosinophilic phenotype are likely to gain real-world benefit from mepolizumab treatment. As such, this evidence can be used to support real-world treatment decisions for this patient population in which such decisions may be confounded by overlapping patient phenotypes.

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Data Availability

Please refer to GSK weblink to access GSK's data-sharing policies and as applicable seek anonymized subject-level data through the link: https://www.gsk-studyregister.com/en/

Disclosures

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