Original Article

REALITI-A Study: Real-World Oral Corticosteroid-Sparing Effect of Mepolizumab in Severe Asthma

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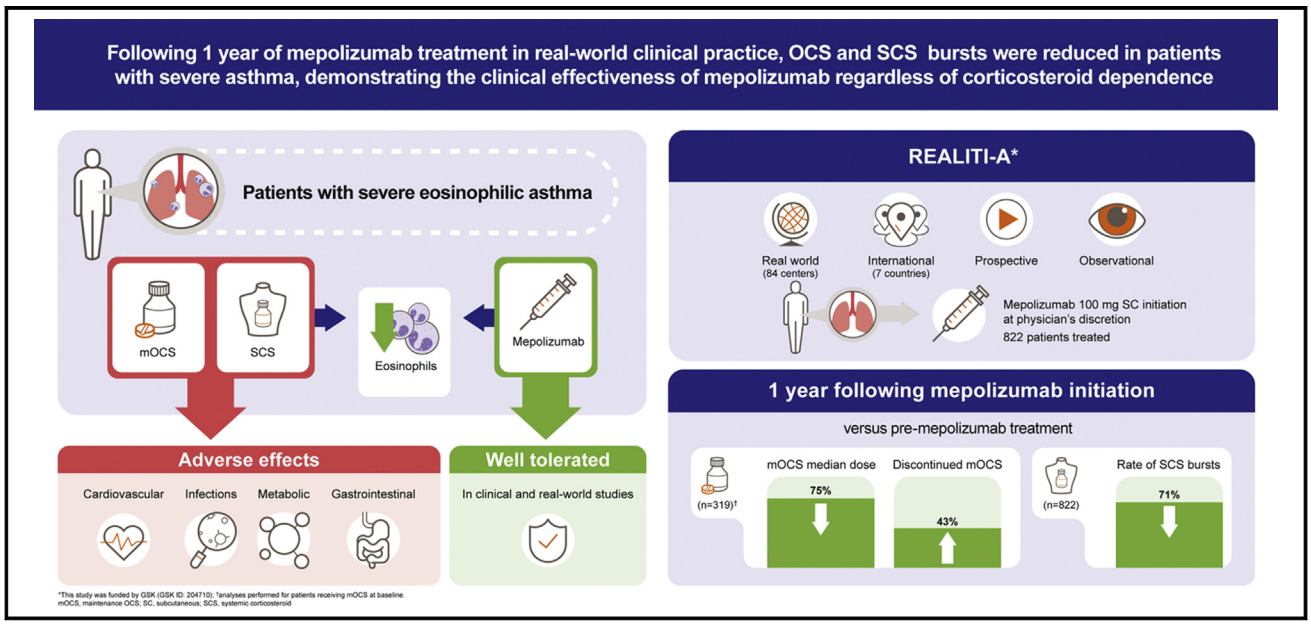
What is already known about this topic? Risks associated with the use of maintenance oral corticosteroids (OCS) and systemic corticosteroid bursts are well-known. Several randomized, placebo-controlled trials involving patients with severe asthma have demonstrated the OCS-sparing effect of mepolizumab.

What does this article add to our knowledge? Data from this large, prospective study translate the OCS-sparing effect of mepolizumab in patients with severe asthma reported across randomized, placebo-controlled trials into real-world clinical effectiveness when used alongside standard of care.

How does this study impact current management guidelines? An OCS-sparing treatment approach for severe asthma is recommended in current guidelines. Our data highlight the clinical effectiveness of mepolizumab as an add-on treatment to reduce maintenance OCS and systemic corticosteroid bursts in corticosteroid-dependent patients.

VISUAL SUMMARY



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Abbreviations used
ACQ- Asthma Control Questionnaire
AE- Adverse event
CSE- Clinically significant asthma exacerbations
ER- Emergency room
HCRU- Health care resource use
mOCS- Maintenance oral corticosteroid
OCS- Oral corticosteroid
RCT- Randomized controlled trial
SC- Subcutaneously
SCS- Systemic corticosteroid
WPAI- Work Productivity and Activity Impairment

BACKGROUND: Patients with severe asthma may require maintenance oral corticosteroids (mOCS) for disease control as well as systemic corticosteroid (SCS) bursts for clinically significant exacerbations. However, mOCS and SCS use are associated with adverse effects, which increases patient disease burden.
OBJECTIVE: To assess the real-world corticosteroid-sparing effect of mepolizumab in patients with severe asthma.
METHODS: REALITI-A was a 24-month international, prospective, observational cohort study involving 84 centers across Europe, Canada, and the United States, with a 1-year pre-post mepolizumab treatment preplanned interim analysis. A total of 822 adults with a clinical diagnosis of asthma and a physician decision to initiate mepolizumab treatment (100 mg subcutaneously) were included. End points included daily mOCS dose at baseline (penultimate 28 days of pretreatment) and 1 year after treatment; percent reduction from baseline in mOCS dose; patients discontinuing mOCS 1 year after treatment; and the rate of clinically significant exacerbations (those requiring OCS for 3 days or more [or parenteral administration], emergency room visit, and/or hospital admission) before and after treatment.
RESULTS: A total of 319 patients received mOCS at baseline (median [interquartile range]: 10.0 [5.0-15.0] mg/d). At 1 year after treatment, median mOCS dose was reduced by 75% (2.5 [0.0-5.0] mg/d); 64% of patients had a reduction in mOCS dose of 50% or greater compared with baseline and 43% discontinued mOCS. Clinically significant exacerbations decreased between pretreatment and posttreatment (rate ratio [95% confidence interval] 0.29 [0.26-0.32]; $P < .001$).
CONCLUSION: This 1-year analysis demonstrates that real-world mepolizumab treatment is clinically effective in patients with severe asthma, providing disease control while reducing the need for mOCS and SCS bursts. **(J Allergy Clin Immunol Pract 2022;10:2646-56)**

Key words: Oral corticosteroids; Mepolizumab; Real-world; Prospective; Eosinophils; Severe asthma; Asthma exacerbations

INTRODUCTION

Severe asthma affects approximately 3% to 10% of patients with asthma and is associated with decreased lung function and poor symptom control.[1,2] Frequent severe exacerbations may occur despite high-dose inhaled corticosteroid treatment plus a second controller and/or systemic corticosteroids (SCS), which can include both long-term maintenance oral corticosteroids (mOCS) and rescue SCS (SCS bursts) for exacerbations.[1] To control symptoms, over 90% of real-world patients with severe

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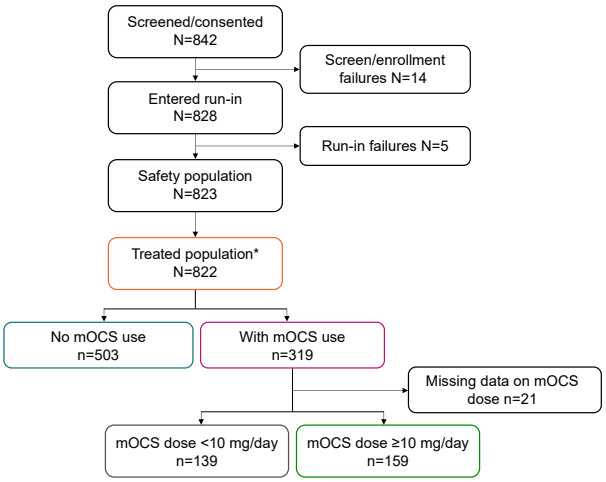

FIGURE 1. Study enrollment status. *One patient began treatment with mepolizumab 300 mg subcutaneously at index (the approved dose for eosinophilic granulomatosis with polyangiitis not severe asthma with an eosinophilic phenotype).[21] This patient was excluded from the treated population.

asthma may also require SCS bursts[3]; 23% to 93% of patients rely on mOCS (mean doses, 9-19 mg/d).[3-9] However, SCS use is well-recognized to be associated with increased risk for SCS-related complications including infections and cardiovascular, gastrointestinal, and metabolic disorders at higher (>6 mg/d) versus lower (≤6 mg/d) doses,[10] further contributing to disease burden.[11-15] Even low cumulative SCS doses (0.5 to <1 g) are associated with an increased risk for SCS-related complications compared with greater than 0 to less than 0.5 g doses.[16] Developing strategies to minimize mOCS and SCS dose and exposure in patients with severe asthma remain a high priority.[2,15-17]

Mepolizumab, a humanized, monoclonal anti-IL-5 antibody, targets IL-5, a key driver of eosinophilic inflammation, significantly reducing blood eosinophil counts.[18-20] Mepolizumab is approved for treatment of severe asthma with an eosinophilic phenotype, eosinophilic granulomatosis with polyangiitis, hypereosinophilic syndrome, and chronic rhinosinusitis with nasal polyps in multiple regions worldwide.[21-23] In randomized controlled trials (RCTs), mepolizumab significantly reduced SCS dose and exposure as well as exacerbations, improved symptom control and health-related quality of life, and was well-tolerated in patients with severe eosinophilic asthma compared with placebo.[8,9,24,25] Finally, mepolizumab was effective in several retrospective real-world studies conducted in broader, less homogeneous, severe asthma populations that more closely reflect patients seen in clinical practice.[6,26-33] However, more robust real-world evidence from prospective, observational studies is needed[34] that assesses the occurrence and magnitude of oral corticosteroid (OCS)-sparing effects in severe asthma.

REALITI-A is a 24-month, international, prospective study assessing the real-world clinical effectiveness of mepolizumab in patients with asthma. It is the largest of a small number of similar regional prospective studies.[5,7,35-37] Results from the 368 early treatment initiators with 1 year of follow-up in the REALITI-A study[5] showed that mepolizumab treatment resulted in clinically meaningful reductions in daily mOCS dose and exacerbations compared with the pre-mepolizumab treatment period, with no unexpected safety signals compared with mepolizumab RCTs.[5,8,9,24,25] Here, we sought to build on the initial REALITI-A study data with an interim analysis of the full study population at 1 year and further explore the real-world impact of mepolizumab on SCS use in patients with severe asthma, with a focus on outcomes stratified by patient baseline mOCS use and dosage.

METHODS

Study design

REALITI-A (GSK ID: 204710) is an international, prospective, single-arm, observational cohort study of patients with asthma who were newly prescribed mepolizumab treatment by their physician. Full study methods were reported previously elsewhere.[5] Briefly, the first dose of mepolizumab 100 mg subcutaneously (SC) was administered on the index date. The pretreatment period consisted of the index date as well as the pre-enrollment and variable-length run-in periods (see Figure E1 in this article's Online Repository at www.jaci-inpractice.org). The pre-enrollment period was defined as 365 days before the enrollment or index date, whichever occurred first. During the pre-enrollment period, patient data were collected retrospectively using medical records and patient recall for the previous year. Medical records of historical exacerbations during the pretreatment were corroborated by patient recall, between clinic visits, to capture instances in which a patient self-medicated at home. Data for the 2 years after the index date (follow-up period) were collected at asthma health care visits (routine or unscheduled) following usual standard of care practices at each participating site. This is an interim analysis of the full study population at 1 year for patients enrolled in December 2016 through October 2019. This was a preplanned interim analysis in which the outcomes of this analysis were designed to assess the primary end point and time point of the study, not to determine a change in the study design or termination of the study.

Patients

Patients who were eligible for enrollment (1) were aged 18 years or older, (2) had a current clinical diagnosis of asthma with a physician decision to initiate mepolizumab treatment, and (3) had relevant medical records for 12 months or greater before enrollment. Patients were excluded if they had received mepolizumab treatment or had participated in an interventional clinical trial in the 12 months before enrollment. Previous use of other biologic medications before study enrollment was permitted. Information regarding ethical approval is detailed in the Study Description in the Online Repository (at www.jaci-inpractice.org).

Outcomes

Outcomes assessed in the full study population at 1 year are described subsequently, with a focus on outcomes of mOCS use and SCS bursts for exacerbations stratified by mOCS use (with/no) and dose (<10 or ≥10 mg/d) subgroups, asthma-related health care resource use (HCRU), Work Productivity and Impairment (WPAI), and Asthma Control Questionnaire-5 (ACQ-5) score, which have not been previously reported for the REALITI-A study.[5]

Maintenance OCS use

Prespecified secondary outcomes relating to mOCS use were the daily mOCS dose and the percent reduction from baseline in mOCS

TABLE I. Patient pretreatment demographics and clinical characteristics at enrollment

Demographic/characteristic	Treated population (N = 822)	Baseline mOCS use		Baseline mOCS dose	
		With mOCS (n = 319)	No mOCS (n = 503)	<10 mg/d (n = 139)	≥10 mg/d (n = 159)
Age, y (mean [SD])	54 (13.6)	54 (13.6)	54 (13.6)	56 (14.1)	52 (13.4)
Female, n (%)	521 (63)	200 (63)	321 (64)	86 (62)	98 (62)
Body mass index, kg/m^2 (mean [SD]) (n = 819)	29.0 (7.24)	29.2 (7.13)	28.9 (7.31)	28.2 (6.63)	30.0 (7.58)
Race, n (%) (n = 821)					
Asian, or Pacific islander	34 (4)	12 (4)	22 (4)	6 (4)	5 (3)
Black	25 (3)	6 (2)	19 (4)	1 (<1)	5 (3)
White	755 (92)	298 (93)	457 (91)	130 (94)	148 (93)
Other	7 (<1)	3 (<1)	4 (<1)	2 (1)	1 (<1)
Smoking history, n (%) (n = 815)					
Never smoked	489 (60)	193 (61)	296 (59)	82 (59)	98 (62)
Former smoker	301 (37)	117 (37)	184 (37)	52 (37)	57 (36)
Current smoker	25 (3)	7 (2)	18 (4)	5 (4)	2 (1)
Smoking pack-years (former/current smoker) (mean [SD]) (n = 217)	17.8 (16.96)	18.7 (17.58)	17.4 (16.67)	17.7 (15.27)	19.9 (20.92)
Asthma duration, y (mean [SD]) (n = 801)	19.7 (15.72)	20.3 (15.15)	19.3 (16.07)	20.9 (15.15)	20.0 (14.95)
Blood eosinophil count, cells/μL* (geometric mean [SD log]) (n = 614)	353 (1.241)	290 (1.395)	404 (1.107)	388 (1.078)	235 (1.586)
mOCS, n (%)	319 (39)	319 (39)	0	139 (44)	159 (50)
OCS dose†, mg/d (median [interquartile range] (n = 298)	10.0 (5.00-15.00)	10.0 (5.00-15.00)	n/a	5.0 (4.00-6.25)	12.9 (10.00-20.00)
Inhaled corticosteroids, n (%)	799 (97)	311 (97)	488 (91)	137 (99)	155 (97)
Inhaled corticosteroid dose‡, μg/d (median) (n = 774)	1,000	1,000	1,000	1,000	1,000
Clinically significant asthma exacerbations in prior 12 mo (mean [SD]) (n = 821)	4.3 (4.05)	4.6 (4.24)	4.2 (3.93)	4.5 (4.33)	4.6 (4.24)
Patients with previous biologic treatment, n (%)	150 (18)	59 (18)	91 (18)	21 (15)	36 (23)
Omalizumab	150 (18)	59 (18)	91 (18)	21 (15)	36 (23)
Duration of omalizumab, mo (mean [SD])	33.6 (35.27)	33.4 (43.38)	33.8 (29.10)	23.1 (23.64)	36.4 (50.09)
Asthma Control Questionnaire-5 score* (mean [SD]) (n = 781)	2.89 (1.324)	3.01 (1.370)	2.81 (1.289)	2.90 (1.357)	3.10 (1.405)
Pre-bronchodilator FEV_1*, mL (mean [SD]) (n = 397)	1,997 (810.1)	2,025 (850.1)	1,979 (783.8)	2,044 (840.9)	2,090 (876.8)
Predicted pre-bronchodilator FEV_1* (%) (mean [SD]) (n = 397)	67.7 (21.06)	68.2 (22.07)	67.3 (20.40)	69.0 (23.23)	68.6 (20.98)
Pre-bronchodilator FVC*, mL (mean [SD]) (n = 396)	2,991 (1,047.1)	3,022 (1,083.4)	2,970 (1,024.4)	3,089 (1,074.6)	3,078 (1,101.5)
Pre-bronchodilator FEV_1/FVC* (mean [SD]) (n = 396)	0.67 (0.13)	0.67 (0.13)	0.67 (0.12)	0.66 (0.13)	0.67 (0.13)
Patients with nasal polyps, n (%)	321 (39)	134 (42)	187 (37)	74 (53)	55 (35)
Primary reason for initiating mepolizumab treatment§, n (%) (n = 753)					
Reduce exacerbations	333 (44)	96 (33)	237 (51)	48 (38)	41 (28)
Improve asthma symptoms	186 (25)	51 (18)	135 (29)	20 (16)	29 (20)
Reduce burden of OCS	171 (23)	132 (45)	39 (8)	54 (42)	68 (47)
Improve quality of life	55 (7)	10 (3)	45 (10)	4 (3)	6 (4)
Improve lung function	8 (1)	2 (<1)	6 (1)	2 (2)	0
Patients with potential systemic corticosteroid −induced comorbidities‖, n (%)					
Cataract	72 (9)	41 (13)	31 (6)	20 (14)	18 (11)
Diabetes	93 (11)	42 (13)	51 (10)	18 (13)	20 (13)
Gastroesophageal reflux disease	309 (38)	127 (40)	182 (36)	52 (37)	67 (42)
Peptic ulcer	17 (2)	9 (3)	8 (2)	5 (4)	4 (3)
Osteoporosis	119 (14)	65 (20)	54 (11)	27 (19)	34 (21)
Fracture	93 (11)	42 (13)	51 (10)	18 (13)	21 (13)

(continued)

TABLE I. *(Continued)*

Demographic/characteristic	Treated population (N = 822)	Baseline mOCS use: With mOCS (n = 319)	Baseline mOCS use: No mOCS (n = 503)	Baseline mOCS dose: <10 mg/d (n = 139)	Baseline mOCS dose: ≥10 mg/d (n = 159)
Glaucoma	30 (4)	13 (4)	17 (3)	7 (5)	5 (3)
Angina pectoris	13 (2)	5 (2)	8 (2)	3 (2)	2 (1)
Myocardial infarction	13 (2)	3 (<1)	10 (2)	1 (<1)	2 (1)
Anxiety	153 (19)	56 (18)	97 (19)	25 (18)	28 (18)
Depression	155 (19)	65 (20)	90 (18)	25 (18)	36 (23)

FEV_1, forced expiratory volume in one second; *FVC*, forced vital capacity; *mOCS*, maintenance oral corticosteroids; *SD*, standard deviation; *n/a*, not applicable.
Patients identified as other included all races that were not categorized as Asian, Native Hawaiian or other Pacific Islander, Black or African American, or White.
*Value taken at mepolizumab treatment initiation or the most recent value available within the 90 days before and including mepolizumab treatment initiation.
†Prednisone-equivalent dose in 28 days before and including mepolizumab treatment initiation (baseline). Missing baseline mOCS data were excluded from the analysis for 21 patients.
‡Fluticasone propionate-equivalent dose in 28 days before and including mepolizumab treatment initiation
§Physician reported.
‖Potential systemic corticosteroid-related adverse events were adapted from those reported in Canonica et al.[40]

dose during the follow-up period. For patients with baseline mOCS use, the proportion discontinuing mOCS therapy during the follow-up period, and the mOCS dose at weeks 53 to 56 were assessed. Changes in mOCS dose were at the discretion of the physician, and dates and doses of mOCS administration were captured in electronic case report forms per patient. The use of mOCS during baseline was defined as the mean daily mOCS dose per patient (expressed as prednisone-equivalent dose in milligrams per day) in the 28-day period before and including the index date. *Post hoc* analyses of daily mOCS dose in the follow-up period and percent reduction in mOCS dose during the follow-up period versus baseline stratified by baseline mOCS use (with/no) and by mOCS dose (<10 or ≥10 mg/d) were also performed.

Systemic corticosteroid bursts for exacerbations

The prespecified primary outcome was the rate of clinically significant asthma exacerbations (CSEs) during pretreatment and follow-up. CSEs were defined as a deterioration in symptom control requiring the use of SCS bursts and/or emergency room (ER) visit and/or hospital admission. Systemic corticosteroid bursts were defined as OCS for 3 days or greater or a single parenteral SCS administration resulting from worsening of asthma symptoms, as per the study protocol. For patients with mOCS use, existing OCS doses were required to be at least doubled to meet the criteria for SCS bursts. Because SCS bursts may be prescribed to manage CSEs, we assessed the impact of mepolizumab treatment on SCS bursts by analyzing the rate of CSEs. We also stratified the rate of CSEs during the follow-up period versus pretreatment by baseline mOCS use and dose (*post hoc* analysis) and analyzed it by time relative to the COVID-19 pandemic (before vs during; *post hoc* analysis) (further details are in the Online Repository). The latter analysis was carried out to determine whether changes in patient behavior owing to the COVID-19 pandemic affected study outcomes.

Other prespecified secondary outcomes

Other secondary outcomes assessed during the pretreatment and follow-up periods were (1) the patterns of mepolizumab use, including adherence, duration, and discontinuation of therapy, and reasons for discontinuation; (2) the rate of patients experiencing exacerbations requiring hospitalization or an ER visit, or hospitalization alone; (3) the likelihood of patients having no exacerbations requiring hospitalization or an ER visit, or hospitalization alone; and (4) asthma-related HCRU (hospital admissions, ER visits, outpatient visits, and asthma medication use). Patterns of work status, as measured by the WPAI questionnaire,[38] change in symptom control, as measured by ACQ-5 score,[39] and total OCS dose were assessed between baseline and every 3 months of follow-up. Full methodologic details of these outcomes are described in the Online Repository. We collected safety data during the follow-up, including treatment-related adverse events (AEs) and treatment-related serious AEs. The relationship between AEs and mepolizumab treatment was determined by the physician. Safety data, ACQ-5 score, and WPAI questionnaire score were also stratified by baseline mOCS use and mOCS dose (*post hoc* analysis).

Statistical analysis

Study power calculations are detailed in the Online Repository and were previously described elsewhere.[5] A treatment policy estimand approach to treatment discontinuation was used in this study, in which all data collected in the follow-up period were included in the analysis regardless of whether participants discontinued mepolizumab treatment. The treated population, used for all effectiveness evaluations, included all enrolled patients who received mepolizumab (approved dose in severe eosinophilic asthma was 100 mg SC) at index. The safety population, used for all safety evaluations, included all enrolled patients who received mepolizumab at any dose. The rate of exacerbations was analyzed using a generalized estimating equation model assuming a negative binomial distribution, with a covariate of treatment period (pretreatment and follow-up). The variance of the estimated mean was corrected for within-patient correlation and the logarithm of time was used 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 via generalized estimating equation, with a covariate of treatment period (pretreatment and follow-up). Changes from baseline in ACQ-5 score and WPAI composite scores were analyzed using mixed-model repeated measures with covariates of time point, country, baseline mOCS use (with/no), and ordinal exacerbation count preexposure (0, 1, 2, 3, and 4 or greater), and included patient data that were analyzable at the given time point.

The pretreatment exacerbation rate was defined over the preenrollment and variable length run-in periods, as shown in Figure E1. Baseline daily mOCS use, prednisone-equivalent OCS

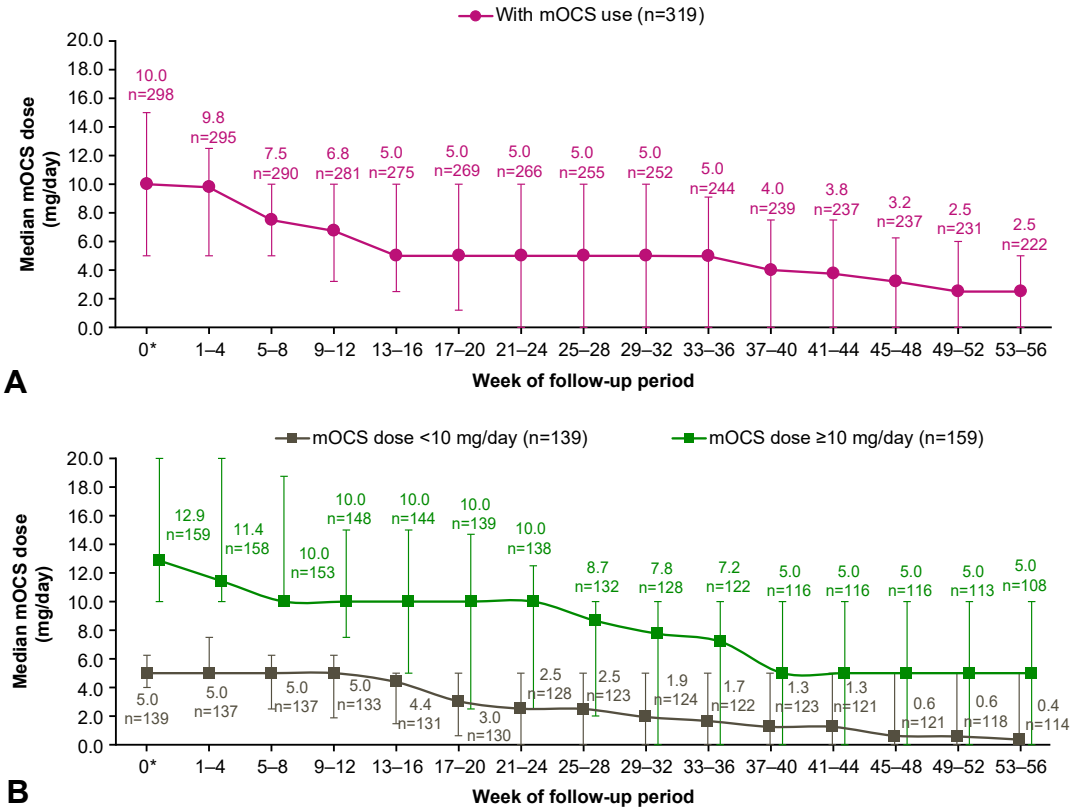

FIGURE 2. Daily maintenance oral corticosteroid (mOCS) dose during follow-up for patients with baseline mOCS use (**A**) and stratified by baseline mOCS doses of less than 10 mg/d and 10 mg/d or greater (**B**). The prednisone-equivalent oral corticosteroid dose is shown (mg/d). Error bars denote interquartile range for daily mOCS dose. Missing baseline mOCS dose excluded 21 patients from the analysis.

dose, and fluticasone propionate-equivalent inhaled corticosteroid dose were defined over the 28 days before and including the date of mepolizumab treatment initiation. For all other assessments, baseline was defined as the most recent value available within the 90 days before and including mepolizumab treatment initiation.

Further information on the statistical approach to each outcome is detailed in the Online Repository. We performed a sensitivity analysis to assess the impact of the COVID-19 pandemic on the study outcomes (see the Online Repository for further details).

RESULTS

Patient population

In total, 823 patients (safety population) and 822 patients (treated population) were included (Figure 1). One patient began mepolizumab 300 mg SC at index (the approved dose for eosinophilic granulomatosis with polyangiitis, and not severe asthma with an eosinophilic phenotype[21]); this patient was excluded from the treated population. Patients were recruited from 84 centers across Belgium, Germany, Italy, Spain, the United Kingdom, Canada, and the United States. The highest proportions of patients were recruited from Italy (30%; n = 244 of 822) and the United Kingdom (24%; n = 200 of 822).

A total of 63% of patients were female (mean [SD] age 54 [13.6] years), and 60% had never smoked (Table I). Mean asthma duration of patients was 19.7 years, geometric mean baseline blood eosinophil count was 353 cells/μL, and 45% of patients had a blood eosinophil count of 500 cells/μL or greater. Within the treated population, 319 patients (39%) had used mOCS during baseline and 298 patients had mOCS dose information (Figure 1). Patient demographics and clinical characteristics were similar across all baseline mOCS use and mOCS dose subgroups, with the exception of baseline blood eosinophil counts, which were higher for patients with no baseline mOCS use and for those receiving the lower category of baseline mOCS dose (<10 mg/d) compared with those with mOCS use and those receiving a higher baseline mOCS dose (≥10 mg/d). In patients with baseline mOCS use, the predominant primary reason for initiating mepolizumab treatment was to reduce OCS burden.

At the 1-year follow-up, 80% of patients continued to receive mepolizumab. Mean (SD) proportion of possible treatment days covered was 87.6% (15.15). The most frequently reported primary reasons for mepolizumab discontinuation were lack of efficacy (6%) and patient decision (4%) (see Table E1 in this article's Online Repository at www.jaci-inpractice.org). Of the 150 patients who continued to receive the first year of mepolizumab treatment after the onset of the COVID-19 pandemic in the first quarter of 2020 (18%), three had a confirmed COVID-19 diagnosis while receiving treatment.

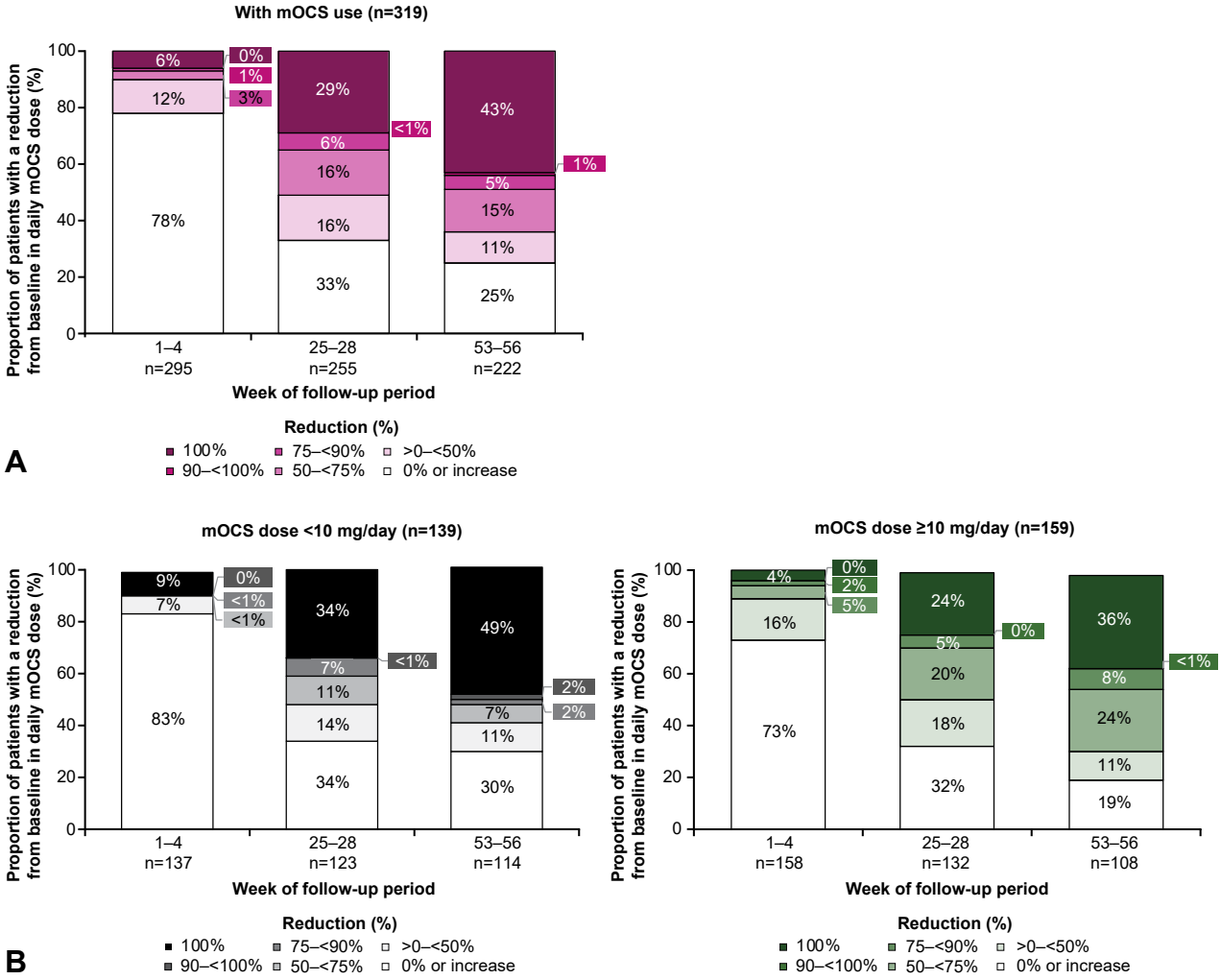

FIGURE 3. Percentage reduction in daily maintenance oral corticosteroid (mOCS) dose between baseline and follow-up for patients with baseline mOCS use (**A**) and stratified by baseline mOCS doses of less than 10 mg/d and 10 mg/d or greater (**B**). The prednisone-equivalent oral corticosteroid dose is shown (mg/d). Missing baseline mOCS dose excluded 21 patients from the analysis.

Maintenance OCS use

In patients with baseline mOCS dose data, median (interquartile range) dose was 10.0 (5.0-15.0) mg/d (Table I and Figure 2, *A*). For those patients, daily median (interquartile range) mOCS dose decreased throughout the follow-up, to 2.5 (0.0-5.0) mg/d during weeks 53 to 56, equivalent to a 75% reduction in median dose from baseline (Figure 2, *A*). Similarly, when patients were stratified by baseline mOCS doses of less than 10 mg/d and 10 mg/d or greater, the mOCS dose decreased from 5.0 and 12.9 mg/d during baseline to 0.4 and 5.0 mg/d during weeks 53 to 56 of the follow-up period, equivalent to a 92% and 61% reduction in median dose, respectively (Figure 2, *B*).

During the follow-up period, the proportion of patients who discontinued daily mOCS increased from 29% during weeks 25 to 28 to 43% during weeks 53 to 56 (Figure 3, *A*); 64% had a 50% or greater reduction in mOCS dose compared with baseline. When patients were stratified by baseline mOCS doses of less than 10 mg/d and 10 mg/d or greater, 49% and 36% of patients, respectively, were able to discontinue the daily mOCS during weeks 53 to 56 (Figure 3, *B*) and 60% and 69% of patients, respectively, had a 50% or greater reduction in mOCS use compared with baseline.

Systemic corticosteroid bursts for exacerbations

The rate of CSEs decreased significantly by 71% between the pretreatment and 1-year follow-up periods ($P < .001$) (Figure 4, *A*). This reduction in CSEs was irrespective of baseline mOCS use, although patients with baseline mOCS doses of less than 10 mg/d trended toward greater improvements compared with patients with baseline mOCS doses of 10 mg/d or greater (Figure 4, *A*). During the follow-up period, patients had an increased odds of having no CSEs compared with the pretreatment period (OR [95% confidence interval (CI)] 13.2 [10.0-17.4]; $P < .001$) (Figure 4, *B*). Patients with less than 10 mg/d and 10 mg/d or greater baseline mOCS doses also had increased odds of having no CSEs during the follow-up period

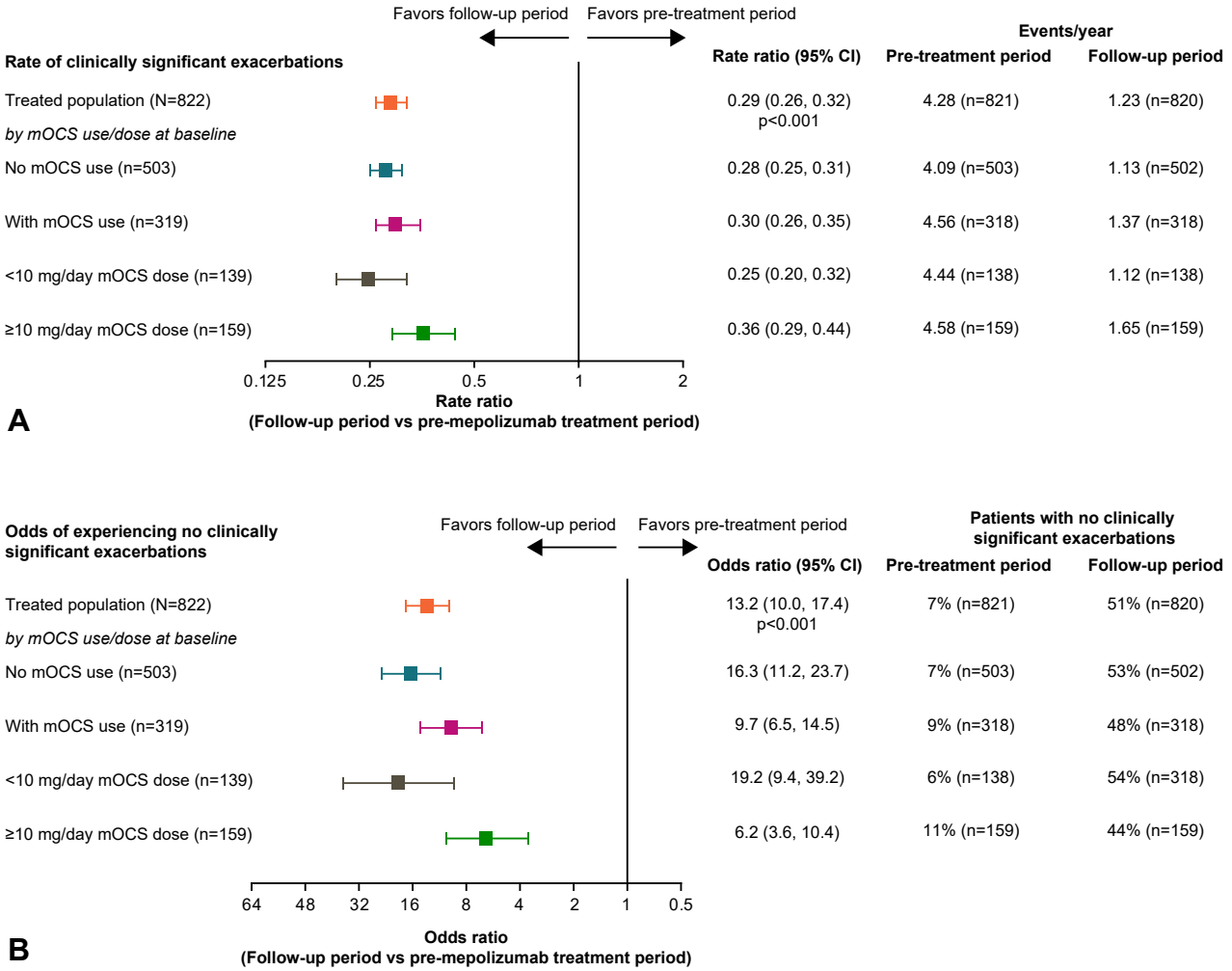

FIGURE 4. Rate of clinically significant asthma exacerbations (**A**) and likelihood of patients experiencing no clinically significant asthma exacerbations (**B**) between pretreatment and follow-up for the treated population and stratified by baseline maintenance oral corticosteroid (mOCS) use and dose. The prednisone-equivalent oral corticosteroid dose is shown (mg/d). Missing baseline mOCS dose excluded 21 patients from the analysis. CI, confidence interval.

compared with the pretreatment period (OR [95% CI] 19.2 [9.4-39.2] and 6.2 [3.6-10.4], respectively) (Figure 4, *B*).

Other prespecified secondary outcomes

Data for other prespecified secondary outcomes including total daily OCS use are detailed in Tables E2 to E4 (in this article's Online Repository at www.jaci-inpractice.org). During the follow-up period, reductions in the rate of exacerbations requiring hospitalization or an ER visit (rate ratio [95% CI] 0.24 [0.20-0.29]; $P < .001$), or hospitalization alone (rate ratio [95% CI] 0.31 [0.24-0.39]; $P < .001$) were observed compared with the pretreatment period irrespective of baseline mOCS use. The odds of patients having no exacerbations requiring hospitalization or an ER visit (OR [95% CI] 3.39 [2.76-4.18]; $P < .001$) or hospitalization alone (OR [95% CI] 3.21 [2.49-4.15]; $P < .001$) increased irrespective of baseline mOCS use. Asthma-related HCRU, including the rates of hospitalization, ER visits, and outpatient visits, significantly reduced during the follow-up versus pretreatment period (rate ratio (95% CI) 0.47 [0.37-0.58], 0.42 [0.33-0.53], and 0.43 [0.37-0.51]; all $P < .001$, respectively). A clinically significant improvement in ACQ-5 score (ie, minimum clinically important difference of 0.5 point or greater reduction[39]) was observed by month 3 compared with baseline (least-squares mean change [95% CI] −1.21 [−1.32 to −1.10]) and was sustained until month 12 (−1.23 [−1.38 to −1.08]); WPAI composite scores also improved by month 12. Improvements in ACQ-5 and WPAI composite scores were similar to the overall population when stratified by patient baseline mOCS use and mOCS dose.

Impact of COVID-19 pandemic on outcomes

A greater decrease in CSEs was observed in the 152 patients who were still participating in the study during the COVID-19 pandemic compared with patients still participating in the study before the COVID-19 pandemic (see Table E5 in this article's Online Repository at www.jaci-inpractice.org). Analysis of study CSE outcomes removing patients who were still participating in the study during the COVID-19 pandemic did not give

TABLE II. AEs and serious AEs related to mepolizumab treatment reported during follow-up for treated population and stratified by baseline mOCS use and dose

Treatment-related AEs	Safety population (n = 823)	Baseline mOCS use		Baseline mOCS dose	
		With mOCS (n = 320)	No mOCS (n = 503)	<10 mg/d (n = 139)	≥10 mg/d (n = 160)
Any treatment-related AEs, n (%)	85 (10)	42 (13)	43 (9)	15 (11)	25 (16)
Leading to discontinuation of mepolizumab	17 (2)	11 (3)	6 (1)	4 (3)	7 (4)
Leading to withdrawal from study*	11 (1)	7 (2)	4 (<1)	3 (2)	4 (3)
Any treatment-related serious AEs, n (%)	6 (<1)	3 (<1)	3 (<1)	0	3 (2)
Fatal	1 (<1)	0	1 (<1)	0	0

AE, adverse event; *mOCS*, maintenance oral corticosteroids.
Treatment-related AEs and treatment-related serious AEs were determined by the investigator.
*All AEs leading to withdrawal from the study also led to discontinuation of treatment with mepolizumab.

significantly different outcomes compared with the analysis of the whole study population (see Table E6 in this article's Online Repository at www.jaci-inpractice.org; compared with Figures 2, *A*; 3, *A*; and 4, *A*; and Table E2).

Safety

Investigator-determined treatment-related AEs were experienced by 85 (10%) patients during the follow-up period. Serious AEs occurred in six patients (<1%) (Table II). Seven patients died during the follow-up period. One patient had a fatally serious AE (diffuse liver malignancy/hepatic cancer) that was considered by the investigator to be related to mepolizumab treatment. A similar proportion of patients experienced investigator-determined treatment-related AEs and serious AEs irrespective of baseline mOCS use or mOCS dose (Table II).

DISCUSSION

To the authors' knowledge, the REALITI-A study is the largest prospective and first international real-world study assessing the effectiveness of mepolizumab in patients with severe asthma. This 1-year analysis of the full patient population showed that the real-world application of mepolizumab in patients with severe asthma substantially reduced daily mOCS dose in corticosteroid-dependent patients. The requirement for SCS bursts was also reduced, as observed by a decreased rate of CSEs. Our findings were consistent for patients receiving lower (<10 mg/d) or higher (≥10 mg/d) baseline mOCS doses. Furthermore, mepolizumab was associated with significant decreases in the rate of exacerbations requiring hospitalizations, or those requiring hospitalization or an ER visit, improved symptom control, and lower work productivity and activity impairment. Overall, we observed no unexpected safety signals in this study. These findings have clinical importance because OCS are still widely used to treat severe asthma despite recognized long-term adverse consequences.[11-15] The results also mirror those for inflammatory diseases in which OCS was historically used, but in which the introduction of biologic therapy as a preferred treatment option has allowed for a substantial reduction in OCS use.[41] This study demonstrates that introducing mepolizumab as part of standard care for severe asthma in a range of health care environments enables a significant reduction in OCS burden.

We found that almost half of corticosteroid-dependent patients discontinued mOCS and approximately two-thirds had a 50% or greater reduction in mOCS dose 1 year after mepolizumab treatment. Importantly, the reductions in mOCS use that these patients experienced were complemented with improved symptom control and fewer CSEs. These findings are consistent with the SIRIUS RCT (NCT01691508) and with smaller, regional, prospective, real-world studies.[25,35-37] Because mepolizumab selectively binds to IL-5, reducing the number of eosinophils in the blood,[8,36,42] and SCS treatment has been shown to correlate inversely with blood eosinophil count,[43] the favorable outcomes observed with mepolizumab treatment attest to the important role of eosinophils in the pathogenesis of severe asthma.[44,45] These results are of high clinical relevance to patients because a primary reason why physicians initiated patients with mepolizumab treatment in REALITI-A was to reduce the burden of OCS. The decreased mOCS and rescue SCS bursts reported for patients with 1 year of mepolizumab treatment highlight the potential benefit of mepolizumab in reducing SCS-related complications, which otherwise may add further disease burden for these patients.[10-14,16]

We reported a 75% reduction in median daily mOCS dose after mepolizumab initiation in corticosteroid-dependent patients. This reduction was greater than the 50% reduction in median daily mOCS dose reported with mepolizumab in mOCS-dependent patients from SIRIUS,[25] potentially as a result of the longer OCS dose reduction period in REALITI-A (12 months) compared with SIRIUS (16 weeks). Our findings are generally consistent with those of other small, regional, prospective, real-world studies.[5,7,35-37] We also reported an SCS-sparing effect of mepolizumab relative to the use of SCS bursts during exacerbations. There was a greater than 70% reduction in CSEs after mepolizumab treatment, paralleled by increased odds of experiencing no CSEs versus the pretreatment period. Our findings complement the 32% to 58% reduction in CSEs reported with mepolizumab versus placebo in RCTs[8,9,24,25] and are in keeping with the early initiators REALITI-A analysis and other prospective real-world data.[5,35-37] The ability to reduce or completely discontinue mOCS was related to the baseline mOCS dose. Patients with a baseline mOCS dose of less than 10 mg/d prednisolone-equivalent demonstrated a 92% reduction from baseline in the median dose, and 49% of these patients completely discontinued mOCS over 1 year of mepolizumab treatment. This contrasts with respective figures of 61% and 36% in patients with a baseline mOCS of 10 mg/d prednisolone-equivalent or greater. This suggests that physicians escalating

patients with severe asthma to mOCS therapy should consider initiating mepolizumab treatment in eligible patients to reduce the mOCS requirement and prevent long-term OCS burden, rather than continuing to escalate.[11-15]

Patients treated in the REALITI-A study, which reflects real-world use, differed from those in RCTs such as the SIRIUS study.[25] Patients in REALITI-A had more severe disease compared with those in SIRIUS and had a higher number of previous exacerbations and higher blood eosinophil counts.[25] The patient population in REALITI-A was also more diverse than that in SIRUS; it included current smokers and ex-smokers with a greater than 10−pack year history.[25] Similarly, although severe asthma was the primary diagnosis for patients included in the REALITI-A study, some patients also had chronic obstructive pulmonary disease or other lung diseases, which were exclusion criteria in the SIRIUS study.[25] Likewise, more patients in REALITI-A had nasal polyps (39%) than did patients in SIRIUS (24%), although this proportion was similar to that observed in other real-world studies of patients with severe asthma (34% to 46%).[29,46,47] Despite these differences, the effectiveness of mepolizumab in REALITI-A was consistent with SIRIUS[25] and previous real-world studies.[5,7,35-37] Together, these findings reveal that the outcomes with mepolizumab from RCTs effectively translate into real-world clinical practice when mepolizumab is used as part of standard care in managing patients with severe asthma. The difference in patient demographics between the SIRIUS RCT and the REALITI-A study, apart from the imposition of strict inclusion and exclusion criteria in the registration RCT study, may reflect local regulatory reimbursement criteria for mepolizumab treatment after its approval compared with preapproval RCTs. Two of the largest recruiting countries for REALITI-A, Italy and the United Kingdom, have the most restrictive reimbursement rules, requiring greater disease severity or higher levels of eosinophilic inflammation, compared with other countries. Despite these differences, our data indicate that mepolizumab reduced SCS use in patients with more severe forms of asthma compared with those recruited to RCTs, and highlights mepolizumab as an effective treatment option for patients whose symptoms and manifestations are considered difficult to treat.[2]

Potential limitations of the REALITI-A as a real-world observational study were discussed previously, including its single-arm and open-label design, which resulted in a lack of comparator for unblinded mepolizumab treatment[5]; an open-label data capture is typical for real-world assessments. In addition, because most patients enrolled in this study were from Western Europe, the study population may not be representative of the global severe asthma population. However, one study, which analyzed data from 11 countries enrolled in the International Severe Asthma Registry consortium, including Kuwait, Greece, Japan, and South Korea, found that 84% of patients with severe asthma had an eosinophilic phenotype.[48] This suggests that REALITI-A study data may well be representative of anticipated global outcomes. REALITI-A was fully recruited by October 2019, before the onset of the COVID-19 pandemic in the first quarter of 2020. Therefore, most patients (82%) had completed the first year of mepolizumab treatment (or had withdrawn from the study) before the onset of the COVID-19 pandemic. Participants typically continued to receive mepolizumab at the usual location, although there was a potential impact of missed dosing in those who were unable to access the treatment location or self-administer mepolizumab at home. The onset of the COVID-19 pandemic affected a small number of patients who were still being observed within the 1-year follow-up period. Interestingly, those patients had lower rates of exacerbation during the pandemic compared with rates recorded when treated with mepolizumab before the onset of the pandemic. These lower exacerbation rates may be a result of measures enforced by governments and health authorities to slow the spread of COVID-19 infection (such as lockdowns, social distancing, mask wearing, and travel restrictions, which resulted in the reduced circulation of pathogens that might trigger an exacerbation, as well as less pollution). Despite the lower rate of exacerbations observed, a sensitivity analysis that excluded patients who were still participating in the study during the COVID-19 pandemic showed consistent results to the analyses reported here.

This interim analysis of data from REALITI-A at 1 year, to the authors' knowledge the largest prospective and first international observational study, demonstrates the real-world benefit of mepolizumab in patients with severe asthma in reducing SCS use (both maintenance and bursts) while improving symptom control. Mepolizumab was well-tolerated with a safety profile consistent with that of previous studies. These findings highlight the SCS-sparing potential of mepolizumab in patients with severe asthma who require SCS bursts and/or mOCS, and may help guide physicians and specialists to make informed treatment decisions for their patients.

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