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Original Article

Treatment Eligibility of Real-Life Mepolizumab-Treated Severe Asthma Patients

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What is already known on this topic? Many patients with severe asthma not meeting criteria of clinical trials investigating mepolizumab are treated with this biological in clinical practice. It is unknown whether these patients respond differently to therapy when compared with trial patients.

What does the article add to our knowledge? Our results indicate that patients deemed ineligible for trial participation could reduce their maintenance oral corticosteroid dosage under mepolizumab therapy to a similar extent as trial patients included in the SIRIUS trial using identical therapeutic endpoints.

How does this study impact current management guidelines? Our findings suggest that novel biological therapies may benefit a broader severe asthma population than initially described in randomized clinical trials.

BACKGROUND: Patients with severe asthma not meeting the strict trial eligibility criteria for mepolizumab are now routinely treated with this biological in clinical practice, but it remains unclear whether these ineligible patients respond differently to mepolizumab treatment.

OBJECTIVE: This study investigated the extent and reasons for trial ineligibility of real-life, mepolizumab-treated patients with severe asthma and compared the characteristics of these patients with trial populations. Subsequently, therapeutic response in ineligible patients was assessed on the basis of oral corticosteroid (OCS) reduction.

METHODS: Trial eligibility, population differences, and therapeutic response were assessed using the baseline characteristics of mepolizumab-receiving patients with severe asthma treated in the Amsterdam University Medical Centres and OCS dose at 6 months for OCS-dependent patients extracted from patients' electronic health records. Eligibility criteria and population characteristics from trials investigating mepolizumab were extracted from their original publications.

RESULTS: A total of 82.4% of 119 mepolizumab-receiving, real-life patients with severe asthma were ineligible for trial inclusion, wherein 42.9% and 39.5% were excluded on the basis of inclusion and exclusion criteria, respectively. The clinical care population was older, more often male and demonstrating a better lung function under lower OCS maintenance dosages in comparison with trial populations. A total of 50% of 66

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No company, organization, or government agency other than Amsterdam UMC provided support or funding for this work. The RAPSODI registry that was used solely for the identification of severe asthma patients was financially supported by GSK and Novartis. However, these parties have not funded the current work.

Conflicts of interest: E. J. M. Weersink reports personal fees from Novartis (advisory board participation); and personal fees from Sanofi Regeneron (advisory board participation), outside the submitted work. G.-J. Braunstahl reports grants and personal fees from GSK (advisory board participation); grants from Teva; grants from Chiesi; grants and personal fees from ALK Abello (advisory board participation); grants from AstraZeneca; personal fees from Sanofi Regeneron (advisory board participation); and personal fees from Novartis (advisory board participation), outside the submitted work. A. T. Brinke reports grants from GSK; grants and personal fees from Teva (advisory board participation); grants and personal fees from AstraZeneca (advisory board participation); and personal fees from Sanofi Regeneron (advisory board participation), outside the submitted work. E. H. D. Bel reports grants and personal fees from Novartis; grants and personal fees from GSK; grants and personal fees from AstraZeneca; grants and personal fees from Sanofi Regeneron; grants and personal fees from Teva; grants and personal fees from Vectura; and grants and personal fees from Boehringer Ingelheim, outside the submitted work. A.-H. Maitland-van der Zee reports grants from GSK (pharmacogenomics of pediatric asthma); grants from Boehringer Ingelheim (breathomics and chronic obstructive pulmonary disease); and personal fees from AstraZeneca (advisory board for benralizumab), outside the submitted work. The rest of the authors declare that they have no relevant conflicts of interest.

Received for publication November 15, 2019; revised March 23, 2020; accepted for publication April 9, 2020.

Available online April 25, 2020.

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2213-2198

https://doi.org/10.1016/j.jaip.2020.04.029

Abbreviations used
COPD- Chronic obstructive pulmonary disease
FDR- False discovery rate
FEV_1- Forced expiratory volume in 1 second
ICS- Inhaled corticosteroids
LABA- Long-acting β-adrenoceptor agonist
LAMA- Long-acting muscarinic receptor antagonist
OCS- Oral corticosteroids
UMC- University Medical Centres

ineligible, OCS-dependent mepolizumab-treated patients were able to reduce their maintenance OCS dosage to ≤5 mg prednisone/day.
CONCLUSIONS: A large proportion of the real-life, mepolizumab-treated population with severe asthma would be excluded from trial participation, and significant differences in population characteristics exist. Regardless, a large fraction of ineligible patients in clinical care can reduce maintenance OCS dosage under mepolizumab therapy. **(J Allergy Clin Immunol Pract 2020;8:2999-3008)**

Key words: *Asthma; Anti-IL-5; Biologicals; Real-life evidence; Type 2 asthma*

Asthma is a prevalent chronic respiratory disease affecting 5% to 10% of the population. Approximately 3.6% of patients with asthma are suffering from a severe form of this condition, wherein, despite the use of high-intensity therapy, asthma symptoms and/or frequent severe asthma exacerbations remain to develop or require chronic usage of systemic corticosteroids to maintain control.[1-3] Furthermore, it is becoming increasingly clear that severe asthma encompasses a large heterogeneity in pathophysiology, clinical expression, and therapeutic responsiveness.[1,4-8] The authorization for marketing of IL-5-targeting biological therapeutics has provided a new avenue of therapy for a subgroup of patients with severe asthma featuring eosinophilic inflammation. Previous research has demonstrated that 25% to 35% of severe asthmatic patients are eligible for this type of therapy on the basis of prescription criteria and/or inclusion criteria.[9-12] However, because of the above-mentioned heterogeneity in the pathology and therapeutic responsiveness of severe asthma, more restrictive eligibility criteria for trial participation were employed in phase II and III trials of these biologicals.[7,13-18] Nevertheless, many patients with severe asthma not meeting these strict trial eligibility criteria are now routinely treated with these therapeutics in clinical practice.[4,7,19] Currently, it is unknown whether these patients behave differently in terms of therapeutic responsiveness in comparison with patients who would have been included in the clinical trials.

We hypothesize that patients treated with mepolizumab in clinical practice differ with respect to patient characteristics and indicators of therapeutic responsiveness from those included in clinical trials. Therefore, the primary aim of this study was to establish the extent of trial ineligibility of mepolizumab-treated patients in a tertiary center for severe asthma and identify predominant reasons leading to trial exclusion. The secondary aims included comparing the characteristics of patients who receive mepolizumab as part of routine clinical care with those of patients included in phase IIb and III clinical trials investigating mepolizumab and exploring differences in therapeutic responses between these patients groups. We used data from mepolizumab-treated patients with severe asthma undergoing treatment in an academic hospital in the Netherlands.

METHODS

Design and study population

We conducted a real-life, retrospective cohort study using data from patients with severe asthma treated with mepolizumab in the Amsterdam University Medical Centres (Amsterdam UMC), location AMC, an academic hospital in the Netherlands. The patients included in the analyses were selected using the Registry of Adult Patients with Severe asthma for Optimal DIsease management (RAPSODI), an ongoing multicenter online register, where patients with severe asthma, as defined by American Thoracic Society/European Respiratory Society criteria,[3] are monitored over time. Subsequently, information regarding clinical characteristics, pulmonary function tests, imaging results, allergies, comorbidities, medication usage, and adverse effects of therapy was extracted from the patients' electronic health records. Cohort entry was defined as the date at which the selected patients received their first mepolizumab administration. Follow-up ended at 6 months after cohort entry, where the reduction of oral corticosteroid (OCS) maintenance therapy, an indicator of therapeutic effectiveness, was assessed for a subgroup of patients using data from the electronic health records (Figure 1). Only patients deemed ineligible for trial participation and who were continuously using mepolizumab (at least 1 administration every follow-up month) for 6 months as well as on OCS maintenance therapy of ≥5 mg per day of prednisone or equivalent at baseline were included for this subgroup analysis.

Determination of trial participation ineligibility

Eligibility for participation in the clinical trials of mepolizumab was determined using the baseline data of the selected mepolizumab-treated patients. Inclusion and exclusion criteria were extracted from the publicly available study protocols of the DREAM, SIRIUS, MENSA, and MUSCA trials (phase IIb and III clinical studies investigating mepolizumab) and are shown in Table I.[13-15,18] Trial ineligibility was defined as: (1) fulfilling at least one of the exclusion criteria; or (2) not fulfilling at least one of the inclusion criteria. Ineligibility of the selected patients to participate in the clinical studies was determined at trial level and overall. Subsequently, predominant reasons for exclusion from trial participation were identified by stratification per inclusion/exclusion criterion.

Characteristics of mepolizumab-treated patients in clinical trials and real-life clinical practice

Patient characteristics of interest included age, gender, body mass index, daily maintenance dose of OCS, prebronchodilator forced expiratory volume in 1 second (FEV_1), and the 5-item Asthma Control Questionnaire score. Patient characteristics were extracted from the original publications and/or clinical study reports of the above-mentioned trials[13-15,18] and from the patients' electronic health records at cohort entry.

Assessment of maintenance OCS dosage reduction

To investigate the therapeutic response to mepolizumab, the reduction in OCS maintenance dose per day was assessed at the 6-month follow-up end date. The maintenance dose applied at 6 months after initiation of monoclonal antibody therapy was

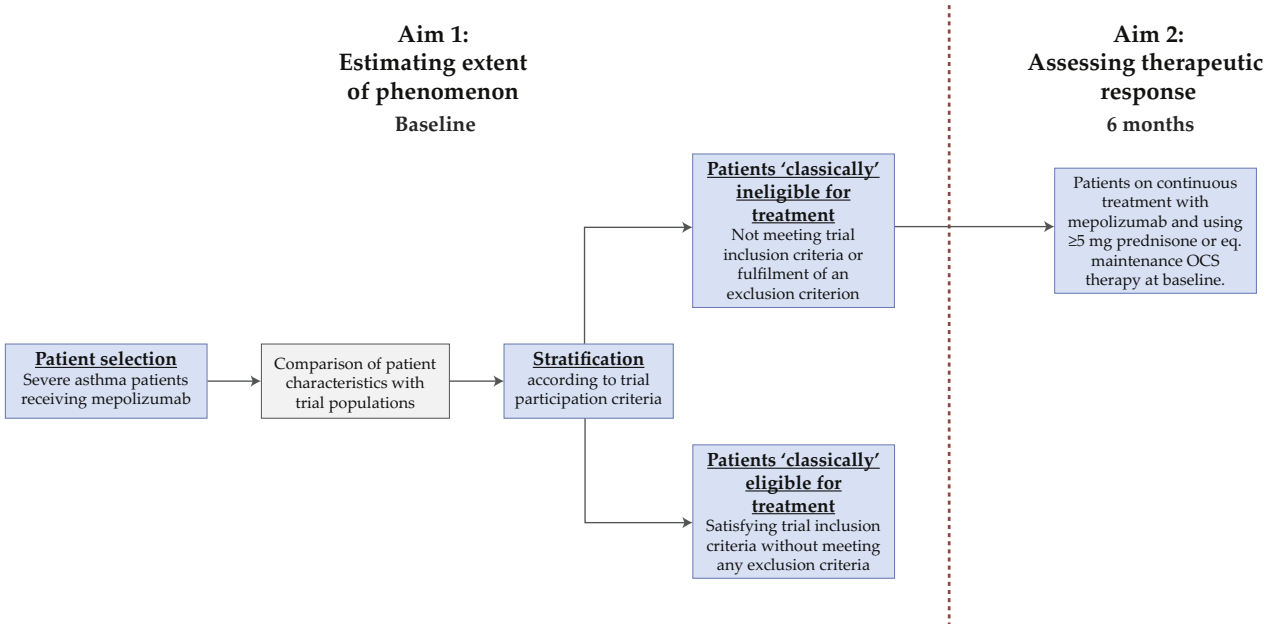

FIGURE 1. Overall design of performed analyses. *OCS*, Oral corticosteroids.

obtained from the electronic patient records. Therapeutic response endpoints of mepolizumab therapy on the basis of reduction of maintenance OCS dosage were defined as follows:

(1) Reduction of the maintenance OCS dosage of at least 50% compared with the prescribed dose at baseline.
(2) Reduction of maintenance dose to less than or equal to 5 mg prednisolone or equivalent per day.
(3) Complete cessation of maintenance OCS usage.

Statistical analysis

Trial ineligibility and reasons for exclusion were summarized using proportions. The baseline characteristics of the selected mepolizumab-treated patients with severe asthma were compared with those included in the clinical trials using a Welch-modified *t*-test and χ^2 tests for continuous and categorical variables, respectively. A false discovery rate (FDR) correction of 10% was applied to reduce the risk of type I errors in the statistical determinations due to the multiple pairwise comparisons. If the original publications and clinical reports of the clinical trials only mentioned the averages and distribution of the individual treatment arms (mepolizumab and placebo), the aggregated mean and distribution were calculated. FDR-corrected *P* values $<.05$ were considered as significant differences. The proportion of patients responding to mepolizumab therapy was assessed using the predefined endpoints. All data preparation and statistical computations were performed using R version 3.4.4.

RESULTS

Trial participation eligibility

Data from 119 mepolizumab-treated patients with severe asthma were included in the eligibility analysis for clinical trial participation. Figure 2 shows the number of patients who would have been excluded from participation in the clinical trials based on the applied inclusion and/or exclusion criteria and the total suitability for participation in these clinical studies per trial. Of the 119 patients included in the primary analysis, 98 (82.4%) were ineligible for trial participation, where 51 (42.9%) did meet at least 1 exclusion criterion and 47 (39.5%) did not fulfill all specified inclusion criteria. Consequently, only 21 (17.6%) of the mepolizumab-receiving patients treated in the Amsterdam UMC would have fulfilled the participation criteria of the DREAM, MENSA, and MUSCA trials. Only 7 (5.9%) of the patients analyzed were found eligible to participate in the SIRIUS trial as a result of the participation requirement with regard to the minimum maintenance OCS dosage of ≥5 mg per day of prednisone or equivalent (Table I).

Selection requirements concerning pulmonary function capacity, the number of eosinophils in peripheral blood, and the prescribed dose of inhaled corticosteroids (ICS) were among the most prevalent reasons for trial ineligibility, with 45.4%, 41.2%, and 31.1% of Amsterdam UMC patients who would have been excluded from trial participation, respectively (Figure 3, *A*). Moreover, only 5.9% of the selected patients met the inclusion criterion concerning an eosinophil blood count of 150 to 300 cells/μL with concomitant maintenance OCS therapy, thereby decreasing the combined ineligibility percentage on the basis of eosinophil concentrations in blood to 27.7% (Figure 3, *A*). Of the trial exclusion criteria, a smoking history of ≥10 pack-years (26.9%), concomitant bronchiectasis (15.1%), and significant cardiovascular comorbidities (5.9%) were the most prevalent characteristics in Amsterdam UMC patients treated with mepolizumab (Figure 4).

Comparison of population characteristics

When comparing baseline characteristics between all trial and mepolizumab-treated Amsterdam UMC patients, statistically significant differences were found, indicating higher age, lower prebronchodilator FEV_1, and lower daily dosage of maintenance OCS therapy as well as differences in the usage of control medications for the Amsterdam UMC population in comparison with the trial populations. In addition, significant differences

TABLE I. Trial eligibility criteria extracted from publicly available study protocols of the SIRIUS, DREAM, MENSA, and MUSCA trials

Criteria	SIRIUS	DREAM	MENSA	MUSCA
Inclusion				
Age ≥12 y and weight ≥45 kg	•	•	•	•
Pre-BD FEV_1 <80% pred (≥18 y) OR pre-BD FEV_1 <90% or FEV_1:FVC-ratio <0.8 (12-17 y)	•	•	•	•
High-dose ICS usage (exactuator dosages; ≥18 y: ≥880 μg/d fluticasone or equivalent 12-17 y: ≥440 μg/d fluticasone or equivalent)	•	•	•	•
Usage of controller-medication (current usage of LABA, LTRA, or theophylline for at least 3 mo)	•	•	•	•
Requirement for regular treatment with maintenance systemic corticosteroids of 5-35 mg per day prednisone or equivalent	•			
Clinical asthma diagnosis on the basis of either:				
(1) >20% variability in diurnal PEF		•	•	•
(2) 12% improvement and 200 mL in FEV_1 after 200 μg salbutamol administration		•	•	•
(3) PC_{20} of max. 8 mg/mL documented in 12 mo preceding study		•	•	•
Two or more exacerbations that required OCS treatment in the preceding year*		•	•	•
Airway inflammation of eosinophilic nature on the basis of either:				
(1) Sputum eosinophils ≥3%		•		
(2) Exhaled nitric oxide ≥50 ppb		•		
(3) Asthma-related elevated blood eosinophil levels ≥300 cells/μL	•	•	•	•
(4) Prompt deterioration of asthma control after ≤25% reduction of maintenance dose of ICS or OCS		•		
Exclusion				
Current smokers and former smokers with a smoking history ≥10 pack-years	•	•	•	•
Presence of a clinically important lung condition other than asthma	•	•	•	•
Subjects who had taken methotrexate, troleandomycin, oral gold, cyclosporine, azathioprine, or any experimental anti-inflammatory therapies within 3 mo of screening		•		
Current malignancy or previous history of cancer in remission for ≤12 mo	•	•	•	•
Unstable liver disease, cirrhosis, and known biliary abnormalities	•	•	•	•
Eosinophilic conditions other than asthma that could lead to elevated eosinophil levels	•	•	•	•
Severe or clinically significant cardiovascular disease uncontrolled with standard treatment	•	•	•	•
Other concurrent medical conditions uncontrolled with standard treatment, endocrine, autoimmune, metabolic, neurological, renal, gastrointestinal, hepatic, hematological, or other system abnormalities	•	•	•	•
Immune deficiency, such as HPV other than explained by corticosteroid usage for asthma	•	•	•	•
Omalizumab usage	•	•	•	•
Poor adherence to medication*	•	•	•	•
Other investigational medication	•	•	•	•
Previous participation in any study of mepolizumab	•	•	•	•

FEV_1, Forced expiratory volume in 1 second; *FVC*, forced vital capacity; *HPV*, human papillomavirus; *ICS*, inhaled corticosteroids; *LABA*, long-acting β-adrenoceptor agonist; *LTRA*, leukotriene receptor antagonist; *OCS*, oral corticosteroids; *PC_{20}*, FEV_1 by 20% of baseline; *PEF*, peak expiratory flow; *ppb*, parts per billion; *pre-BD*, prebronchodilator; *pred*, predicted.
*Criterion has not been tested in the current study.

were found in gender distribution corresponding with a higher amount of males in the Amsterdam UMC trial populations, with the exception of the population included in the SIRIUS trial (Table II).

Assessment of maintenance OCS dosage reduction in ineligible patients

With respect to therapeutic response endpoints in patients who would have been ineligible for trial participation and were continuously treated with mepolizumab over the 6-month follow-up period (N = 66 patients), 28 (42.4%) patients halved their daily maintenance dose of OCS therapy. Moreover, 33 (50%) patients were able to reduce their daily OCS maintenance dose to a maximum of 5 mg per day of prednisone or equivalent and 14 (21.2%) patients demonstrated complete cessation of maintenance therapy with OCS (Figure 5). The median daily maintenance OCS dosage was 10 mg at baseline and decreased to a median daily dosage of 5 mg after 6 months of continuous therapy in these patients (interquartile range: 10-19.4 and 1.6-10 mg, respectively; reduction in individual and overall maintenance OCS dosage per day are illustrated in Figure E1, available in this article's Online Repository at www.jaci-inpractice.org).

DISCUSSION

We found that a large proportion of 82.4% of the mepolizumab-receiving patients with severe asthma undergoing treatment in the Amsterdam UMC did not meet the inclusion and/or exclusion criteria of the mepolizumab trials. Of these patients, 42.9% would not have been eligible for the trial participation on the basis of meeting exclusion criteria. This was

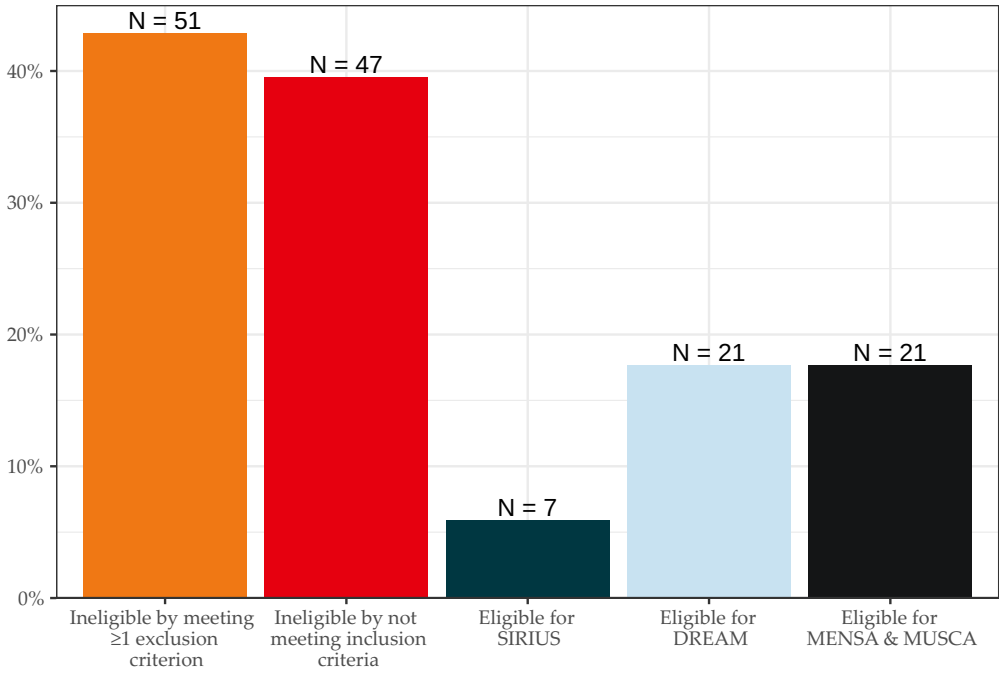

FIGURE 2. Total eligibility and ineligibility of 119 mepolizumab-receiving patients with severe asthma undergoing treatment in the Amsterdam University Medical Centres for participation in clinical trials of mepolizumab. Trial participation criteria were extracted from publicly available study protocols of the SIRIUS, DREAM, MENSA, and MUSCA trials. Trial ineligibility was defined as: (1) fulfilling at least one of the exclusion criteria; or (2) not fulfilling at least one of the inclusion criteria.

mainly driven by coexistence of comorbidities of the airways and cardiovascular system as well as a smoking history of more than 10 pack-years. With regard to the inclusion criteria, 39.5% of patients did not meet all requirements, with better lung function values, lower ICS dose, and lower blood eosinophil concentrations primarily resulting in trial exclusion. There were statistically significant differences in population characteristics between the mepolizumab-treated severe asthma population in the Amsterdam UMC and trial populations, with the Amsterdam UMC population being predominantly older and more often male. Moreover, patients showed better lung function values accompanied by a significantly lower maintenance dosage of OCS, which may suggest a less severe, mepolizumab-treated population in clinical practice in comparison with the populations included in clinical trials. Hence, the real-life severe asthma population appears to be different from the trial populations, thereby underlining the limited representativeness of the latter for the severe asthma population in clinical care. Interestingly, we also found that 50% of OCS-dependent patients who would have been ineligible for trial participation were able to reduce their maintenance dosage of OCS to a maximum of 5 mg per day after 6 months of continued mepolizumab treatment. In addition, 21.2% of these patients demonstrated complete cessation of OCS maintenance therapy. These results are roughly similar to those found in the SIRIUS trial, which used identical endpoints for assessing therapeutic efficacy.[15] Therefore, our findings suggest that not only carefully selected patients in clinical trials, but also patients with eosinophilic airway inflammation with a history of smoking, significant comorbidities, and/or fixed airway obstruction could be candidates for and may benefit from treatment with mepolizumab.

Our findings suggest that observed outcomes in clinical trials of mepolizumab may be similar for patients with severe asthma treated in the clinical care setting.[13-15,18] Yet, it also complements these studies because patients originally considered unsuitable on the basis of the trial participation criteria were also included in our study. Moreover, our study also expands on previous studies investigating the eligibility anti-IL-5 treatment of patients with severe asthma. Although the aim of these studies partially overlaps with that of the current study, treatment eligibility was based on mepolizumab prescription criteria and/or a limited of trial inclusion criteria. Consequently, more lenient criteria sets were applied within these studies to assess eligibility and thereby explain the slightly lower found eligibility criteria of 17.6% in the current study in comparison with the 25% to 35% found in these studies.[9-12] Moreover, as the cohort analyzed in this study consisted entirely of mepolizumab-treated patients with severe asthma, the current design of the study allowed us to demonstrate discrepancies in population characteristics amongst the trial and real-life, mepolizumab-treated patients with severe asthma. Furthermore, the current work is the first study, to our knowledge, using data acquired in clinical care to assess the real-life therapeutic efficacy of monoclonal antibody therapies for eosinophil-mediated severe asthma. However, several active projects exist in which such real-life data from patients with severe asthma are collected on a large scale, such as the Severe Heterogeneous Asthma Research collaboration, Patient-centered (SHARP) and the International Severe Asthma Registry (ISAR) projects.[20-22] Our results are consistent with a recent study assessing trial eligibility in the Wessex Severe Asthma Cohort (WSAC), which found that 9.8% (range, 3.5%-17.5%) of patients would have been eligible for inclusion in trials investigating

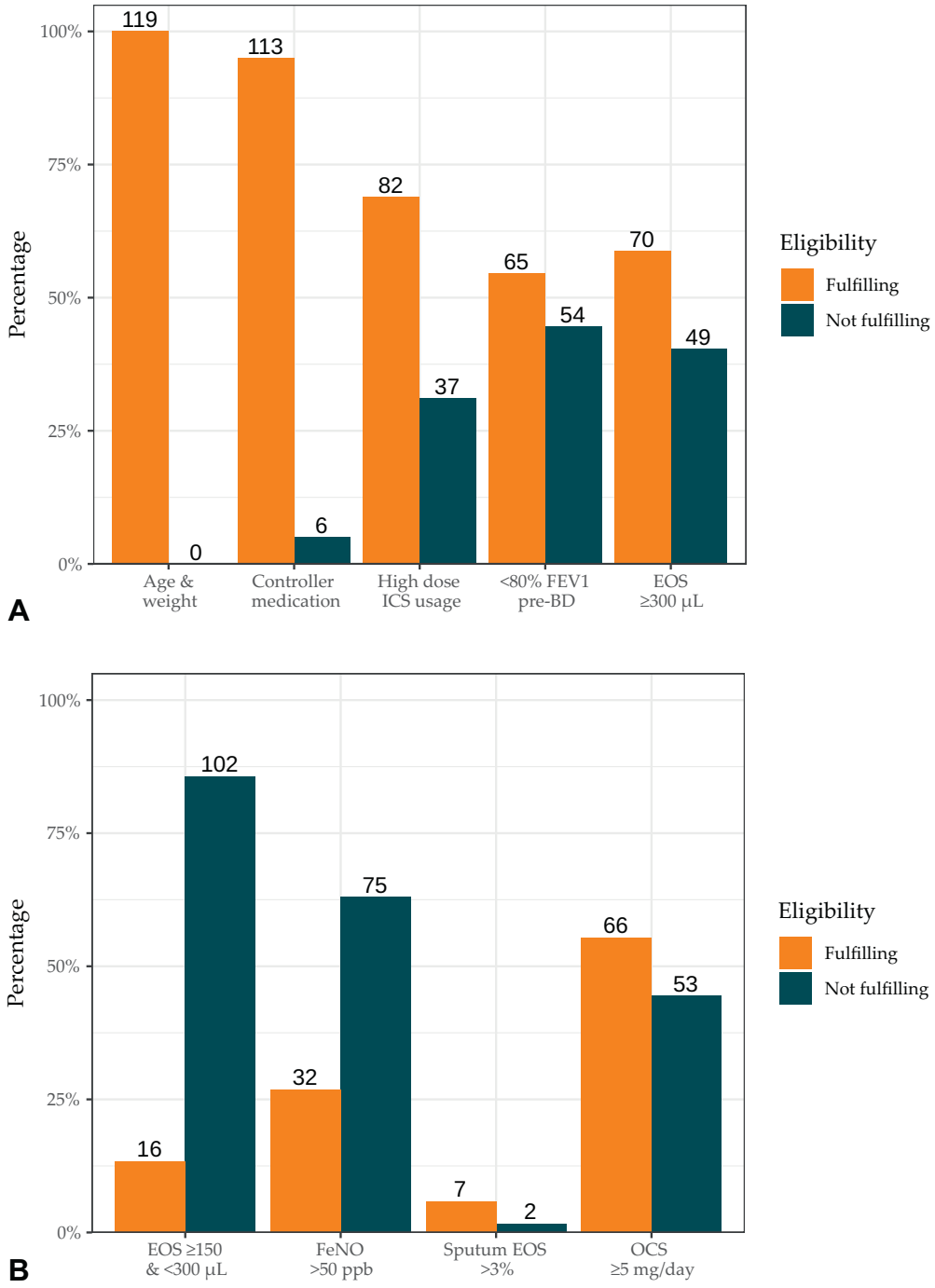

FIGURE 3. Fulfillment of inclusion criteria of clinical trials of mepolizumab by 119 mepolizumab-receiving patients with severe asthma undergoing treatment in the Amsterdam University Medical Centres on the basis of main and additional inclusion criteria illustrated in (**A**) and (**B**), respectively. *EOS*, Eosinophils; *FeNO*, fraction of exhaled nitric oxide; FEV_1, forced expiratory volume in 1 second; *ICS*, inhaled corticosteroids; *OCS*, oral corticosteroids; *pre-BD*, prebronchodilator.

IL-5 targeting biologicals.[19] Furthermore, the limited representativeness of the real-life asthma populations does not only occur with anti-IL-5 therapies. For instance, Mansur et al demonstrated that only 27% of the patients with severe asthma in the Birmingham Regional Severe Asthma Centre (BRSAS) registry were eligible for anti-IgE therapy initiation when applying the National Institute for Health and Care Excellence (NICE) omalizumab usage criteria.[23] Regardless of these criteria, a good clinical response was achieved in 82% of these patients after 16 weeks of treatment, which is also in line with previous reports.[24-26] Moreover, restrictive selection is not only reserved for randomized clinical trials of severe asthma, but also occurs frequently in chronic obstructive pulmonary disease (COPD) studies. In a study on treatment eligibility for long-acting airway

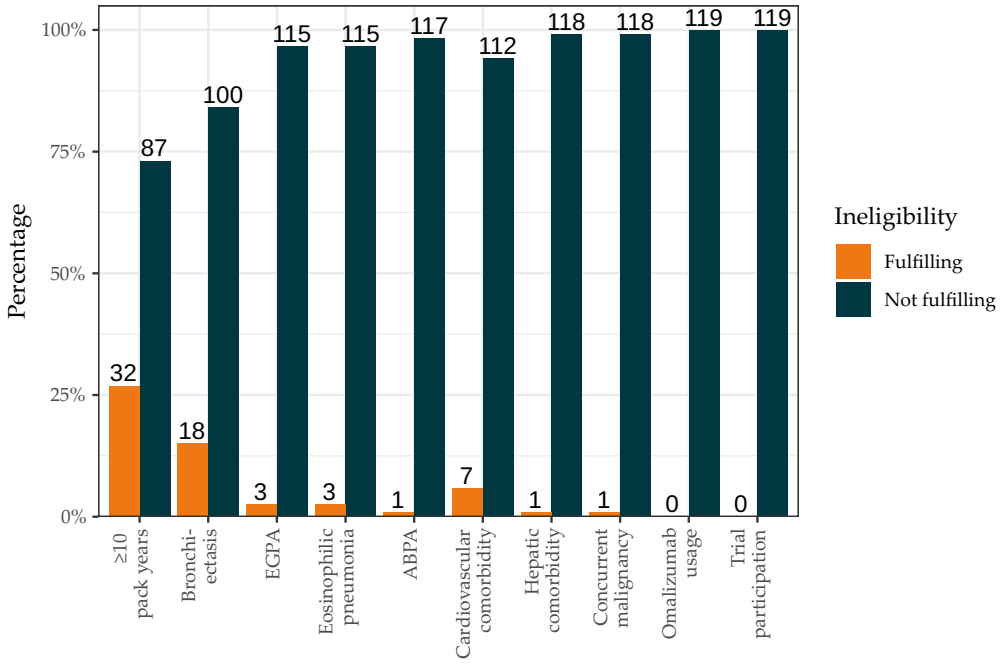

FIGURE 4. Extent of ineligibility on the basis of exclusion criteria of clinical trials investigating mepolizumab by 119 mepolizumab-receiving patients with severe asthma undergoing treatment in the Amsterdam University Medical Centres. *ABPA*, allergic bronchopulmonary aspergillosis; *EGPA*, eosinophilic granulomatosis with polyangiitis.

TABLE II. Characteristics of mepolizumab-receiving patients with severe asthma undergoing treatment in the Amsterdam UMC at cohort entry and trial populations included in clinical trials investigating mepolizumab at baseline

	SIRIUS	DREAM	MENSA	MUSCA	RAPSODI
Participants (N)	135	616	576	551	119
Age (y)	49.9 ± 12.3***	48.6 ± 11.3***	50.1 ± 14.3***	51 ± 13.5***	58 ± 13.8
Female gender, N (%)	74 (55)	387 (63)**	329 (57)*	325 (59)*	54 (45)
BMI (kg/m^2)	28.7 ± 6	28.5 ± 6	27.8 ± 5.8	28.2 ± 6.4	28.3 ± 5.5
FEV_1 pre-BD (L)	1.9 ± 0.8***	1.9 ± 0.7***	1.8 ± 0.7***	1.7 ± 0.6***	2.4 ± 0.9
ACQ5 score	2.1 ± 1.2	2.4 ± 1	2.2 ± 1.2	2.2 ± 1.1	2.4 ± 1.2
LABA usage, N (%)	21 (16)***	590 (96)	85 (15)***	547 (99)***	112 (94)
LAMA usage, N (%)	26 (19)	45 (7)***	85 (15)***	114 (21)*	36 (30)
LTRA usage, N (%)	57 (42)**	160 (26)	280 (49)***	222 (40)**	29 (24)
ICS dosage (μg/d)†	NA	NA	NA	NA	1240 ± 840
Maintenance OCS dosage (mg/d)	12.8 ± 6.7***	17.4 ± 16.8***	13.2 ± 11.9***	13 ± 10.8***	8.1 ± 10
Blood eosinophils (cells/μL)†	NA	NA	NA	NA	0.459 ± 0.382

Data expressed as mean ± SD, unless otherwise specified. *P* values ≤ .05 when compared with the Amsterdam UMC population. Statistically significant differences between trial populations and the Amsterdam UMC population with *P* values ≤.05, .01, and .001 are denoted with *, **, and ***, respectively.
ACQ5, Five-item asthma control questionnaire; *BMI*, body mass index; *FEV_1*, forced expiratory volume in 1 second; *ICS*, inhaled corticosteroids; *LABA*, long-acting β-adrenoceptor agonist; *LAMA*: long-acting muscarinic receptor antagonist; *LTRA*, leukotriene receptor antagonist; *NA*, not available; *OCS*, oral corticosteroid; *pre-BD*, pre-bronchodilator; *SD*, standard deviation; *UMC*, University Medical Centres.
†No statistical tests were performed on this variable.

dilators, only 23% of patients with COPD included in the respiratory-focused Optimum Patient Care Research Database(OPCRD) met the participation criteria of 31 clinical trials investigating long-acting β-adrenoceptor agonist (LABA)/long-acting muscarinic receptor antagonist (LAMA) therapy in patients with COPD.[27] A similar phenomenon was observed by Woodcock et al in the Salford Lung Study (SLS), an open-label, randomized pragmatic trial assessing the safety and effectiveness of fluticasone furoate and vilanterol in patients with COPD seen in routine clinical practice. A follow-up analysis of trial eligibility based on the participation criteria of 6 randomized clinical trials investigating the LABA/ICS combination resulted in a limited eligibility of 30%.[28,29] Therefore, our results are consistent with previous studies, and similar discrepancies between the patient population in clinical care and trial populations also exist in other respiratory research areas.

Nevertheless, the results of the current study should be viewed in the light of a few limitations. First, extrapolation of the results

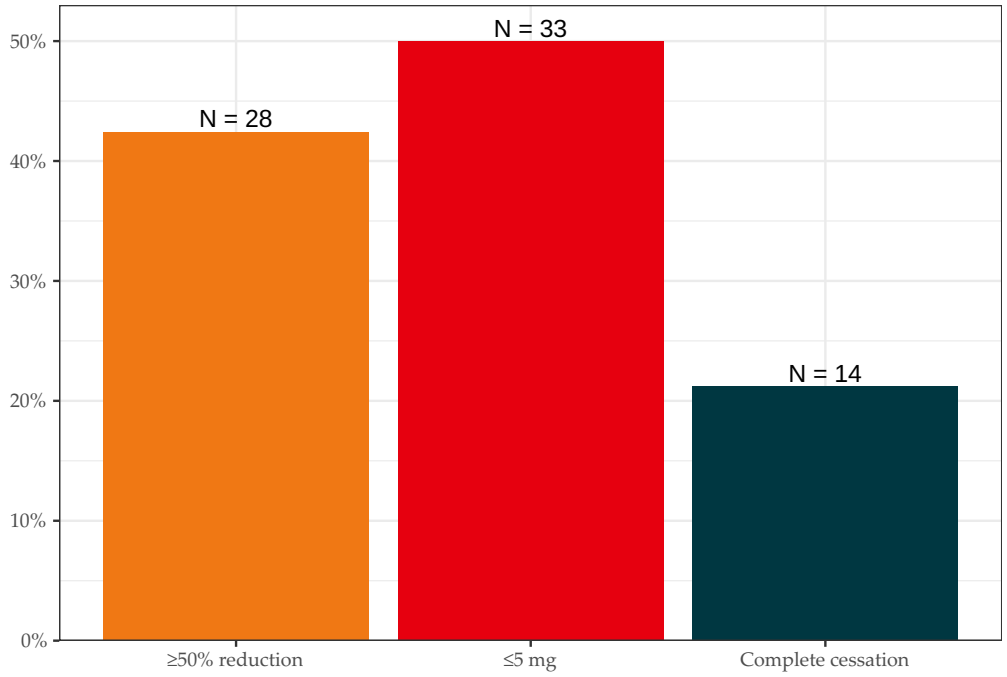

FIGURE 5. Reduction of OCS maintenance dosage per day at 6 months of 66 OCS-dependent, mepolizumab-receiving patients with severe asthma undergoing treatment in the Amsterdam University Medical Centres. Patients ineligible for trial inclusion and using at least 5 mg maintenance dose OCS were included in the analysis. *OCS*, Oral corticosteroids.

found in this study may be complicated as all the patients included in the analyses are treated in one academic hospital with an asthma expertise center for (severe) asthma. Therefore, initiation of therapy is decided by clinical experts in the field of severe asthma, whereby factors potentially contributing to asthma complaints being treated as fully as possible or excluded before considering monoclonal antibody treatment. However, it is unclear how representative this type of care concerning severe asthma treatment is for the care provided in other hospitals. Secondly, because of the lack of reliable data on exacerbation frequency in the patients' electronic health records, we could not assess the trial exacerbation inclusion criterion in our study. It should be noted, however, that excluding exacerbation rate from the analysis merely overestimates the established percentage of patients with severe asthma eligible for trial participation, but does not further affect the interpretation of these results. Furthermore, patients could also be excluded from clinical trial participation for poor adherence to therapy, as indicated in Table I. Nonetheless, a large proportion of patients with severe asthma remain excluded from trial inclusion ineligible for trials. Thirdly, because of the difference in aim and the associated differences in eligibility criteria to the other clinical trials analyzed, the inclusion of the DREAM trial in the analysis could possibly have led to deviations in the results. However, both stratification of eligibility status per trial as shown in Figure 2 and exclusion of the DREAM trial in our analyses did not change the outcomes. Therefore, this potential limitation appears not to have influenced the results of the analyses performed. Fourthly, because of the nature of the retrospective design and use of a severe asthma registry for subject selection that did not have information on patients not treated with biologicals, we did not have access to a comparison group. Consequently, a statistical assessment of the differences in therapeutic outcomes relating to mepolizumab treatment without controlling for confounding factors using an appropriate comparison group was not possible, although we aimed to provide descriptive results rather than to draw conclusions on the effectiveness of mepolizumab treatment in routine clinical care. Fifthly, the applied follow-up period of 6 months may have resulted in selection of patients who are likely to respond favorably to mepolizumab therapy, because their physicians decided not to discontinue therapy during the follow-up period. However, the follow-up period employed is broadly in line with the assessment period of 4 and 6 months for clear and unclear response to initiation of biological therapy recommended in the Global Initiative for Asthma guidelines or severe asthma. Therefore, the applied follow-up period appears to be appropriate for a valid assessment of mepolizumab therapy response.[1] Lastly, because we did not have access to the original raw data of previously published randomized clinical trials, it is unknown whether trial population characteristics were normally distributed, which may have led to an overestimation of differences in characteristics of the analyzed mepolizumab-treated severe asthma population found in clinical care and trial populations.

Randomized clinical trials evaluate the pharmacological efficacy of drugs under highly controlled, restrictive conditions, where the highly selective inclusion of patients reduces confounding factors and achieves a high internal validity of effects. Consequently, the results obtained from randomized clinical trials cannot necessarily be generalized to a larger, more complex, unselected patient population in the clinical care setting. Nevertheless, these studies often play an important role in drug policy making via the incorporation in treatment guidelines, possibly overgeneralizing results.[1,23] We show that randomized clinical trials investigating monoclonal antibody

treatment in type 2 severe asthma mainly exclude patients on the basis of diagnostic criteria, which further impedes the external validity of outcomes via hyperselection of subjects.[13-15,18] Patients not meeting these clinical characteristics may possibly exhibit a therapeutic response on the use of anti-IL-5 biologicals. Accordingly, those patients featuring signs of eosinophilic airway inflammation might benefit from therapy with mepolizumab, regardless of clinical expression of the disorder or comorbidities. Therefore, health care professionals may consider an investigational treatment with IL-5 targeting antibodies in patients with severe respiratory disease and increased blood eosinophil concentrations. Because the biological trait of increased blood eosinophil concentrations could be more important for achieving therapeutic response to mepolizumab than the clinical expression of respiratory disease, clinicians may consider to adopt a precision-based treatment approach wherein the choice of therapy initiation with anti-IL-5 therapies in patients with respiratory disease should not be based on the clinical diagnosis, but rather on the presence or absence of eosinophilic inflammation. However, it should be noted that future studies need to be conducted to determine the suitability of this treatment approach in this patient population.[6,7,30-34] Furthermore, it is important to be aware of the limitations of randomized clinical trials and the potential generalization of the outcomes of these studies in the development of treatment algorithms.

In conclusion, we demonstrated that a large proportion of the patients with severe asthma treated with mepolizumab in routine clinical care would be excluded from participation in clinical trials. We also demonstrated that differences exist in characteristics between the studied clinical care population and the trial populations. No major descriptive differences appear to exist in therapeutic response indicators based on the reduction in maintenance dosage of OCS between patients who meet eligibility criteria of randomized clinical trials investigating mepolizumab and patients not meeting these criteria. Therefore, novel biological therapies may benefit a broader severe asthma target population than initially described in randomized clinical trials. Furthermore, future research should focus on gathering more effectiveness endpoints data under suboptimal research conditions in the form of large-scale real-life cohort studies, which better mimics the context of routine clinical care than randomized clinical trials. To gain more insight into the real-life effectiveness of drugs in different patients, it is important to collect large amounts of data from clinical care, and, where possible, on an international level and from primary, secondary, and tertiary health care settings.[20,21,35]

Acknowledgments

The RAPSODI registry was financially supported by GSK and Novartis. Nonetheless, the pharmaceutical companies had no influence on the data collection, data processing, study design, result interpretation, the writing of this manuscript, and the decision to publish. We would like to thank Dr. K. J. Velthove for her critical review of this manuscript.

L. B. Richards, C. Longo, E. H. D. Bel, and A. H. Maitland-van der Zee contributed to conceptualization. L. B. Richards, J.J.M.H. van Bragt, and R. Aarab contributed to data acquisition. L. B. Richards contributed to formal analysis. L. B. Richards, J.J.M.H. van Bragt, C. Longo, A. H. Neerincx, Els J.M. Weersink, E. Bel, and A.-H. Maitland-van der Zee contributed to interpretation of results. L. B. Richards contributed to writing (original draft). J.J.M.H. van Bragt, R. Aarab, C. Longo, A. H. Neerincx, J. K. Sont, Els J.M. Weersink, G.-J. Braunstahl, A. ten Brinke, E. H. D. Bel, and A.-H. Maitland-van der Zee contributed to review and editing.

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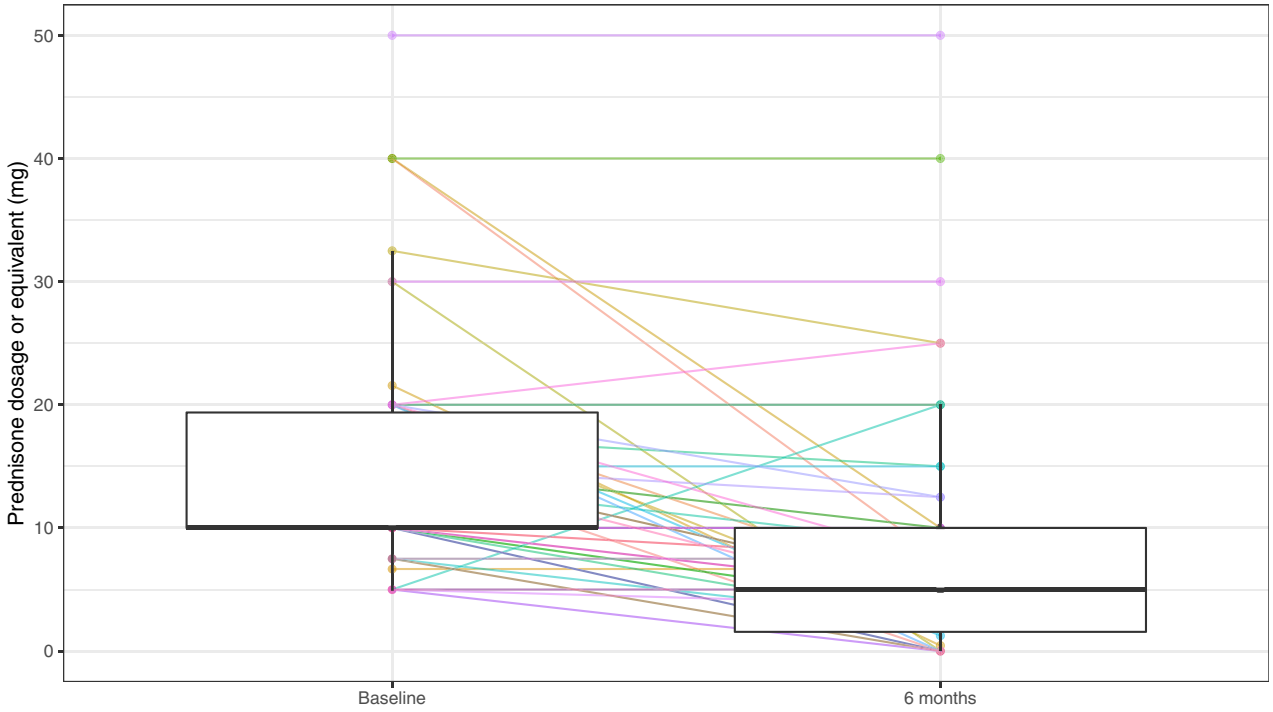

FIGURE E1. Individual and overall (median with IQR) OCS maintenance dosage per day at baseline and 6 months of 66 OCS-dependent, mepolizumab-receiving patients with severe asthma undergoing treatment in the Amsterdam UMC. Patients ineligible for trial inclusion and using at least 5 mg maintenance dose OCS were included in the analysis. *IQR*, Interquartile range; *OCS*, oral corticosteroids; *UMC*, University Medical Centres.