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Original Article

Long-Term Weight Changes After Starting Anti−IL-5/5Ra Biologics in Severe Asthma: The Role of Oral Corticosteroids

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What is already known about this topic? Many patients with severe asthma are overweight or obese, possibly related to a dose-dependent side effect of oral corticosteroids (OCSs). Anti−IL-5/5Ra biologics significantly reduce OCS use, but their long-term effects on weight are unknown.

What does this article add to our knowledge? In our large severe asthma cohort, anti−IL-5/5Ra therapy was associated with minor weight loss after 2 years. The higher the OCS exposure before and the greater the OCS reduction during anti −IL-5/5Ra therapy, the more weight the patients lose.

How does this study impact current management guidelines? Although healthy weight is important to both the patient and the health care provider, most patients do not achieve this despite biological treatment, suggesting that additional interventions are needed if weight change is desired.

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Abbreviations used
BMI- body mass index
OCS- oral corticosteroid
RAPSODI- Registry of Adult Patients with Severe asthma for Optimal DIsease management

BACKGROUND: Many patients with severe asthma are overweight or obese, often attributed to unintentional weight gain as a side effect of oral corticosteroids (OCSs). Anti−IL-5/5Ra biologics significantly reduce OCS use, but their long-term effects on weight are unknown.

OBJECTIVES: To examine (1) weight change up to 2 years after anti−IL-5/5Ra initiation in subgroups on the basis of maintenance OCS use at start of treatment and (2) whether cumulative OCS exposure before or changes in OCS exposure during treatment are related to weight change.

METHODS: Real-world data on weight and cumulative OCS dose from adults included in the Dutch Registry of Adult Patients with Severe asthma for Optimal DIsease management before and at least 2 years after starting anti−IL-5/5Ra were analyzed using linear mixed models and linear regression analyses.

RESULTS: For the included 389 patients (55% female; mean body mass index, 28 ± 5 kg/m^2; 58% maintenance OCS), mean weight decreased −0.27 kg/y (95% CI, −0.51 to −0.03; P = .03), with more weight loss in patients with maintenance OCS use than in those without maintenance OCS use (−0.87 kg/y [95% CI, −1.21 to −0.52; P < .001] vs +0.54 kg/y [0.26 to 0.82; P < .001]). Greater weight loss at 2 years was associated with higher cumulative OCS dose in the 2 years before anti−IL-5/5Ra initiation (β = −0.24 kg/g; 95% CI, −0.38 to −0.10; P < .001) and, independently, greater reduction in cumulative OCS dose during follow-up (β = 0.27 kg/g; 95% CI, 0.11 to 0.43; P < .001).

CONCLUSIONS: Anti−IL-5/5Ra therapy is associated with long-term weight reduction, especially in patients with higher OCS exposure before treatment and those able to reduce OCS use during treatment. However, the effect is small and does not apply to all patients, and so additional interventions seem necessary if weight change is desired. **(J Allergy Clin Immunol Pract 2023;11:2748-56)**

Key words: *Severe asthma; Eosinophilic asthma; Airway inflammation; Biologics; Corticosteroids; Body mass index; Extrapulmonary traits; Multicenter*

INTRODUCTION

Asthma is a complex and heterogeneous disease with major impact on patients and society. In particular, patients with severe eosinophilic asthma are at risk of poor symptom control and severe exacerbations as well as drug side effects.[1] Severe eosinophilic asthma is characterized by extensive eosinophilic inflammation in the airways, which until recently could be controlled only by recurrent or daily use of oral corticosteroids (OCSs).[2-4] As has been known for decades, long-term use of OCSs is associated with a multitude of side effects, including unintentional weight gain.[5] These side effects are dose-dependent, leading to increasing appreciation of data on cumulative OCS exposure.[6-8]

Fortunately, the introduction of biologics has provided opportunities for improved treatment and management of severe eosinophilic asthma.[9] Three of the currently approved biologics (mepolizumab, reslizumab, and benralizumab) target IL-5/5Ra, one of the cytokines that drives the eosinophilic inflammation.[10] Anti−IL-5/5Ra biologics improve asthma control, reduce exacerbations, and are highly successful in reducing (cumulative) OCS exposure.[11-15]

From a patient's perspective, the importance of OCS reduction is undeniable.[6] Many patients with severe asthma report concerns about OCS side effects,[16] and "less OCS use" emerged as one of their main treatment goals. Unlike the side effects that are of most concern to clinicians, such as diabetes and osteoporosis, the side effect of OCSs that bothers many patients is weight gain, along with insomnia, mood disturbances, and skin changes.[17]

Indeed, many patients with severe asthma present with substantial overweight.[4] Although reasons such as asthma-induced exercise limitation may play a role, unintentional weight gain in these patients is often coattributed to OCS use. The resulting higher body mass index (BMI) has a considerable effect on patients' quality of life and daily functioning, as well as future health, because it may further complicate asthma.[18] Treatments with a beneficial effect on weight are of interest because studies have consistently shown that weight loss improves asthma control and has a positive impact on patients' quality of life.[19-23]

As relevant as weight seems to be, there is only limited data on weight change after the initiation of the potent OCS-sparing anti−IL-5/5Ra biologics. Previous studies with less than 1-year follow-up time suggested no or marginal changes in BMI.[24,25] However, the weight change over a longer period after anti−IL-5/5Ra initiation is not known. Furthermore, it has never been explored whether weight loss is more pronounced in patients with higher OCS exposure before anti−IL-5/5Ra initiation, particularly to be expected in patients who use OCS on a daily basis, or in patients who manage to reduce their OCS exposure during anti−IL-5/5Ra treatment. Answering these questions is important because it can provide information about what to expect from such treatment on an important disease burden—affecting outcome from the patient's perspective.

Therefore, in the present real-world, nationwide study, we examined weight before and up to 2 years after initiation of anti−IL-5/5Ra biologics in patients with severe asthma with or without OCS maintenance therapy at the start of treatment. We also evaluated the relationship between weight change and, first, the cumulative OCS dose over a 2-year period before anti−IL-5/5Ra treatment and, second, the anti−IL-5/5Ra−induced changes in cumulative OCS dose in the 2 follow-up years.

METHODS

Study design and patient population

This was a nationwide, real-world registry-based cohort study. The study population consisted of patients with severe asthma included in the Dutch Registry of Adult Patients with Severe asthma for Optimal DIsease management (RAPSODI). The registry

contains data from 19 hospitals and includes annually recorded patient-level data (CASTOR EDC platform [electronic case report form], Amsterdam, The Netherlands) and electronic patient questionnaires (PatientCoach, Leiden University Medical Center, Leiden, The Netherlands). In addition, dispensing data of systemic corticosteroids (ATC code H02AB) during 2 years before and 2 years after anti−IL-5/5Ra initiation were requested from each patient's pharmacy, as described previously.[7] We made sure the patient consented to the Dutch National Exchange Point to ensure that medication possibly dispensed at other pharmacies was captured. For the present study, we included data of all patients who initiated an anti−IL-5/5Ra biologic (mepolizumab, reslizumab, or benralizumab) between December 2015 and January 2019 and who were followed for at least 24 months after initiation of this anti−IL-5/5Ra biologic. All patients were diagnosed with severe asthma according to the European Respiratory Society/American Thoracic Society guidelines[26] and were on high-dose (>500 μg fluticasone equivalent/d) inhaled corticosteroids combined with additional controller medication. We distinguished 2 groups of patients in the analysis: patients who did and those who did not receive maintenance OCS at anti−IL-5/5Ra treatment initiation. Patients were excluded if no follow-up data or pharmacy data were available, or if inflammatory comorbidities requiring OCS treatment (eg, rheumatoid arthritis) were registered in RAPSODI.

The Medical Ethics Review Committee of the Academic Medical Centre approved the objectives of RAPSODI, including future studies using data from the registry (reference no. W15_066 #15.0078). Informed consent was obtained at registry enrollment.

Study variables

Study variables at the moment of anti−IL-5/5Ra initiation (baseline) included (1) demographic characteristics (age, sex, smoking history, and BMI); (2) asthma-specific characteristics (age of onset, atopic status, and exacerbation rate); (3) questionnaire scores (the Asthma Control Questionnaire and the Asthma Quality of Life Questionnaire[27,28]); (4) reported comorbidities (nasal polyposis, adrenal insufficiency, obstructive sleep apnea syndrome, gastroesophageal reflux disease, and diabetes mellitus); (5) lung function (prebronchodilator FEV_1); (6) inflammatory markers (blood eosinophils and fractional exhaled nitric oxide); and (7) data on medication (receiving OCS maintenance treatment, cumulative OCS dose preinitiation and postinitiation, type of biologic, and previous biologic use).

The cumulative OCS dose (in grams) was calculated as the sum of the number of tablets dispensed multiplied by the strength (in milligrams per tablet) in months −24 to 0 and months 0 to 24.[7] The change in cumulative OCS dose was calculated by subtracting the cumulative OCS dose before treatment initiation from the cumulative OCS dose after treatment initiation.

Outcome measures

The effect of weight was assessed using weight data retrieved from RAPSODI at the start of anti−IL-5/5Ra treatment and at 1- and 2-year follow-up. Weight was assessed in the lung function laboratory during a clinical visit, and weight by the following BMI categories was also assessed: healthy weight (<25 kg/m^2), overweight (≥25 and <30 kg/m^2), and obesity (≥30 kg/m^2).[29]

Statistical analysis

Continuous variables were expressed as mean ± SD or median and interquartile range when applicable. Categorical variables were expressed as absolute numbers and percentages. Differences between patients with and those without maintenance OCS use were analyzed using independent *t* tests, the Mann-Whitney *U* test, or the χ^2 test, as appropriate.

To examine the primary research question, that is, weight change in the 2 years after the start of anti−IL-5/5Ra treatment, a linear mixed-effects model analysis was performed, including a random intercept, with adjustments for age, sex, and smoking history (β coefficients with 95% CI and predicted means at baseline, 1 year, and 2 years, on the basis of mean age, sex, and smoking history). In addition, weight change was examined for the subgroups on the basis of maintenance OCS use at anti−IL-5/5Ra initiation. The interaction term for Time × OCS use was explored in the mixed model to formally assess differences in effects between these subgroups. Changes in BMI categories for patients with and without maintenance OCS use before and at 2 years after the start of anti−IL-5/5Ra biologics were visually explored using a Sankey diagram and were analyzed using the McNemar test. In addition, we categorized weight change into classes considered clinically relevant: weight loss (≥5% baseline weight), no change (<5% decrease or increase in baseline weight), or weight gain (≥5% baseline weight).[20,30] A sensitivity analysis was performed in patients with a BMI greater than or equal to 25 kg/m^2 to explore whether findings are robust when analyses are restricted to patients with overweight or obesity.

To explore the secondary research question, that is, the role of OCS exposure on weight change, a linear regression analysis was performed to investigate (1) associations of the total weight change over the 2 years with cumulative OCS dose in the 2 years before anti−IL-5/5Ra treatment and (2) anti−IL-5/5Ra−induced changes in the cumulative OCS dose over the 2 years of follow-up. Weight change was defined as weight at 2 years minus weight at baseline, and the analysis was adjusted for age, sex, and smoking history.

All statistical analyses were performed using IBM SPSS version 28.0 (Armonk, NY). A *P* value of less than .05 indicated statistical significance.

RESULTS

Patients

Of the 878 patients included in RAPSODI on January 1, 2021, 462 patients initiated anti−IL-5/5Ra biologic treatment (mepolizumab, reslizumab, or benralizumab) before January 1, 2019, and were followed for 2 or more years. Baseline and follow-up data from 389 patients were used in the analysis (Figure 1). Table I provides the baseline characteristics at anti−IL-5/5Ra initiation. Most patients had nonatopic asthma with an adult onset of disease. Overall, the patients showed poor symptom control (median Asthma Control Questionnaire score, 2.2) and 75% of patients had 2 or more exacerbations in the year before treatment initiation. Median cumulative OCS dose in the 2 years before treatment initiation was 2.72 g (interquartile range, 1.15-5.54 g), and 58% of patients received maintenance OCS at anti−IL-5/5Ra initiation. As compared with patients who did not use OCS as daily therapy, patients on maintenance OCS use had a higher number of pack years, reported reflux more often, and had lower levels of fractional exhaled nitric oxide and eosinophils in peripheral blood, but similar exacerbation rates and levels of FEV_1.

At the time of anti−IL-5/5Ra initiation, the mean BMI for the total study population was 27.8 ± 5.0 kg/m^2, with 31% of patients classified as healthy weight, 44% as overweight, and 25% as obese. Weight did not differ between patients with and those without maintenance OCS.

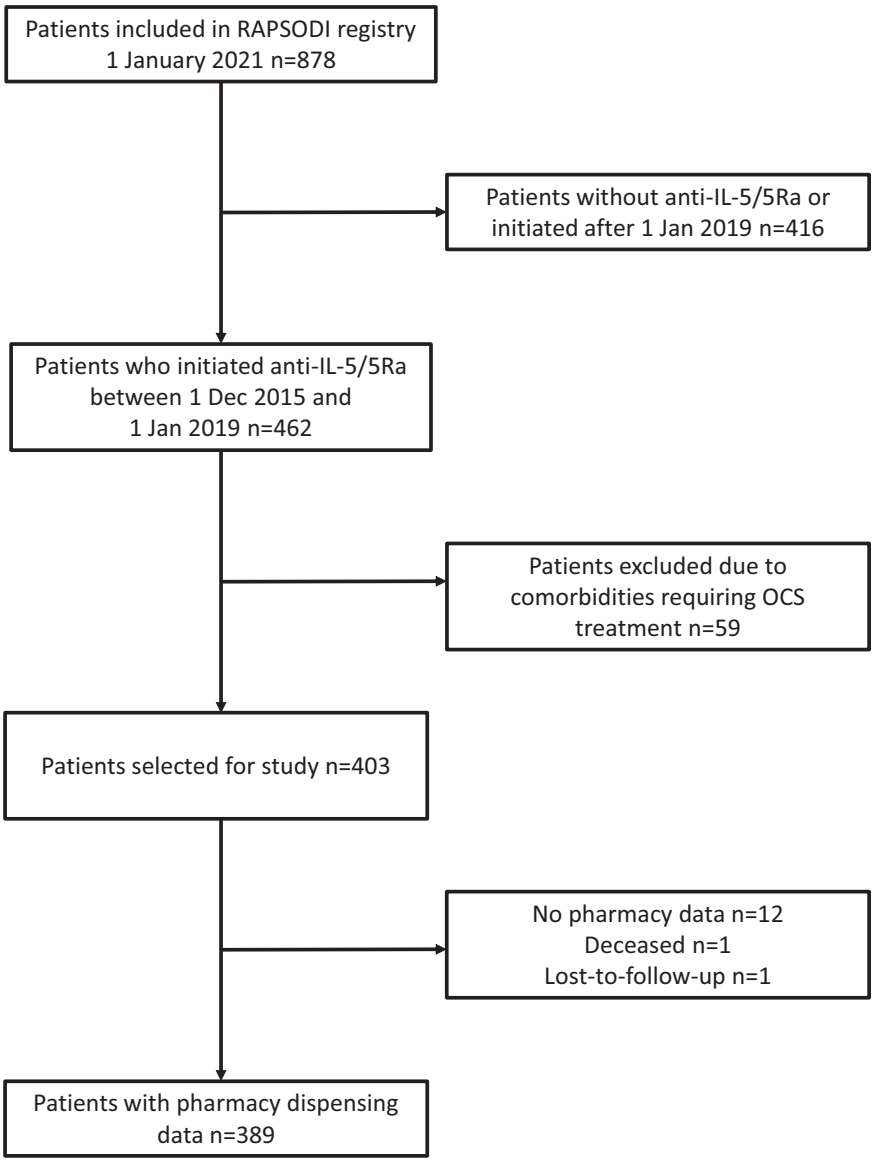

FIGURE 1. Flow diagram for selection of study population.

Weight change after anti−IL-5/5Ra initiation

Mean follow-up time after anti−IL-5/5Ra initiation was 11.8 ± 2.8 months for the 1-year assessment and 23.9 ± 3.5 months for the 2-year assessment. Mean change in the cumulative OCS dose between 2 years before and 2 years after treatment initiation was −1.1 ± 3.4 g.

Two years after the start of anti−IL-5/5Ra treatment, weight had decreased significantly in the total population by −0.27 kg/y (95% CI, −0.51 to −0.03; $P = .03$) (Figure 2, *A*). Of note, we observed significantly different effects on weight change for the subgroups on the basis of maintenance OCS use at anti−IL-5/5Ra initiation (Figure 2, *B*). In the maintenance OCS group, we observed a weight reduction of −0.87 kg/y (95% CI, −1.21 to −0.52; $P < .001$), whereas there was a weight increase of 0.54 kg/y (95% CI, 0.26 to 0.82; $P < .001$) in the group without maintenance OCS use at anti−IL-5/5Ra initiation.

In the overall study population, 20% of patients achieved a weight loss of at least 5% of their baseline weight (see Table E1 in this article's Online Repository at www.jaci-inpractice.org), with a mean weight loss of −8.1 ± 4.1 kg. Of these patients, 86% was on OCS maintenance therapy and 84% had a BMI greater than or equal to 25 kg/m^2. In addition, 16% of patients had a clinically relevant weight gain (mean, 7.0 ± 3.6 kg), with 46% of them using maintenance OCS and 64% of them having a BMI greater than or equal to 25 kg/m^2.

As a sensitivity analysis, the main analysis was repeated in patients with a BMI greater than or equal to 25 kg/m^2 and showed similar results for the subgroups, namely, significant weight loss in patients receiving OCS maintenance therapy and significant weight gain for patients without maintenance OCS use (see Table E2 in this article's Online Repository at www.jaci-inpractice.org). For the total group of patients with a BMI

TABLE I. Baseline characteristics for the total study population and by subgroups on the basis of maintenance OCS use at anti−IL-5/5Ra initiation

Characteristics	Total (N = 389)	On maintenance OCS (n = 225)	No maintenance OCS (n = 164)
Patient characteristics			
Age (y)	55.3 ± 13.0	55.3 ± 13.3	55.5 ± 12.7
Sex: female	212 (54.5)	118 (52.4)	94 (57.3)
Weight (kg)	82.2 ± 16.0	82.3 ± 15.5	82.0 ± 16.6
BMI (kg/m^2)	27.8 ± 5.0	27.7 ± 4.8	27.9 ± 5.3
Healthy weight (<25 kg/m^2)	122 (31.4)	68 (30.2)	54 (32.9)
Overweight (≥25 and <30 kg/m^2)	171 (44.0)	107 (47.6)	64 (39.0)
Obesity (≥30 kg/m^2)	96 (24.7)	50 (22.2)	46 (28.0)
Positive smoking history	163 (41.9)	96 (42.7)	67 (41.4)
Pack years, median (interquartile range)	10.0 (5.0-20.0)	12.8 (5.8-23.0)	8.0 (4.0-18.0)*
Disease-specific characteristics			
Late onset (age ≥12 y)	293 (75.5)	173 (76.9)	120 (73.2)
Atopy	170 (43.7)	97 (44.3)	73 (46.2)
No. of exacerbations			
0-1	89 (22.9)	53 (24.0)	36 (22.6)
2-5	213 (54.8)	117 (52.9)	96 (60.4)
>5	78 (20.1)	51 (23.1)	27 (17.0)
ACQ score, median (interquartile range)	2.2 (1.5-3.0)	2.33 (1.5-3.0)	2.2 (1.8-3.1)
AQLQ score, median (interquartile range)	4.7 (4.0-5.5)	4.72 (4.0-5.5)	4.6 (3.8-5.6)
Reported comorbidities			
Nasal polyposis	197 (50.6)	116 (56.9)	81 (55.5)
Adrenal insufficiency	6 (1.5)	5 (2.2)	1 (0.6)
Gastroesophageal reflux	68 (17.5)	49 (29.2)	19 (16.0)*
Obstructive sleep apnea syndrome	43 (11.1)	25 (15.1)	18 (14.4)
Diabetes mellitus	17 (4.4)	14 (6.2)	3 (1.8)*
FEV_1% predicted prebronchodilator	75.7 (21.4)	76.1 (21.2)	75.1 (21.6)
FENO (ppb), median (interquartile range)	40.0 (23.3-75.8)	36.0 (21.0-66.0)	56.0 (26.0-80.0)†
Blood eosinophil level (10^9/L), median (interquartile range)	0.42 (0.20-0.67)	0.35 (0.10-0.61)	0.50 (0.32-0.71)‡
Asthma pharmacological characteristics			
OCS maintenance at anti−IL-5/5Ra initiation	225 (57.8)	225 (100)	0 (0)
Cumulative OCS dose 2 y before anti−IL-5/5Ra initiation (g), median (interquartile range)	2.72 (1.15-5.56)	5.07 (2.92-7.17)	1.08 (0.45- 1.82)‡
Start type of anti−IL-5/5Ra biologic			
Mepolizumab	325 (83.5)	188 (83.6)	137 (83.5)
Reslizumab	42 (10.8)	26 (11.6)	16 (9.8)
Benralizumab	22 (5.7)	11 (4.9)	11 (6.7)
Biologic-naive	315 (81.0)	184 (81.8)	131 (79.9)

ACQ, Asthma Control Questionnaire; *AQLQ*, Asthma Quality of Life Questionnaire; *FENO*, fractional exhaled nitric oxide; *ppb*, parts per billion.
Values are mean ± SD or absolute number (%), unless otherwise specified.
*$P < .05$ (compared with group on maintenance OCS).
†$P < .01$ (compared with group on maintenance OCS).
‡$P < .001$ (compared with group on maintenance OCS).

greater than or equal to 25 kg/m^2, no significant weight change was observed (−0.07 kg/y; 95% CI, −0.38 to 0.25; $P = .67$).

Figure 3 illustrates the change in BMI categories 2 years after initiation of anti−IL-5/5Ra treatment in subgroups of patients with or without maintenance OCS use at baseline. The results show that in the subgroup using maintenance OCS, the proportion of patients with healthy weight changed from 30% before to 42% 2 years after starting anti−IL-5/5Ra treatment ($P < .001$). No such effect was seen in the patients without maintenance OCS.

Role of OCS exposure on weight change

In the total population, greater weight loss after 2 years of follow-up was observed in patients exposed to a higher cumulative OCS dose in the 2 years before initiation of anti−IL-5/5Ra treatment ($\beta = -0.24$ kg/g; 95% CI, −0.38 to −0.10; $P < .001$) (Figure 4, *A*). In addition, independent of this previous OCS exposure, patients who achieved greater reductions in the cumulative OCS dose in the follow-up years lost more weight over the 2 years ($\beta = 0.27$ kg/g; 95% CI, 0.11 to 0.43; $P < .001$) (Figure 4, *B*).

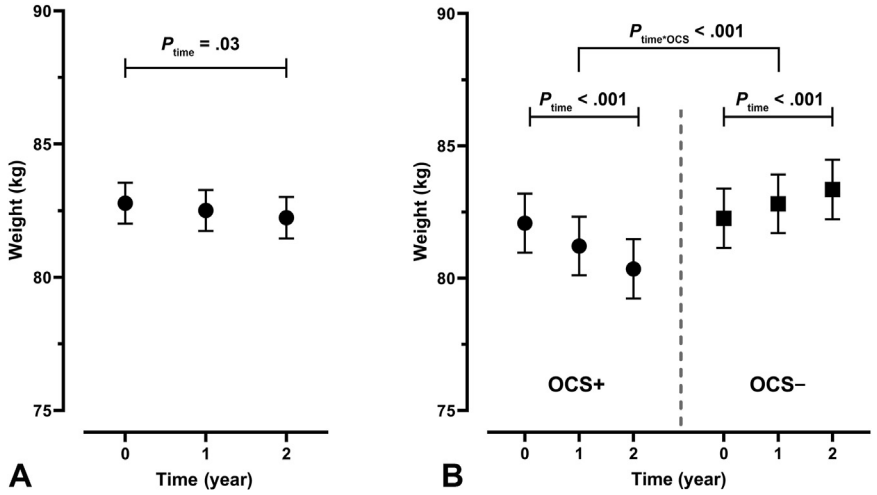

FIGURE 2. Weight change 2 years after anti−IL-5/5Ra initiation. Mean weight during 2-year follow-up for (**A**) the total study population and (**B**) subgroups with vs subgroups without maintenance OCS use at anti−IL-5/5Ra initiation. Error bars indicate SEs for predicted means on the basis of linear mixed models adjusted for age, sex, and smoking history. *OCS+*, Patients with maintenance OCS use at anti−IL-5/5Ra initiation; *OCS−*, patients without maintenance OCS use at anti−IL-5/5Ra initiation.

DISCUSSION

This real-world study in patients with severe eosinophilic asthma shows that treatment with anti−IL-5/5Ra biologics is associated with long-term weight reduction, an important outcome from a patient's perspective, which seems to be related to OCS use. Patients with maintenance OCS use before starting anti−IL-5/5Ra biologics achieved a greater reduction in weight as compared with patients without maintenance OCS use. In addition, a higher cumulative OCS dose before anti−IL-5/5Ra initiation and a reduction in OCS exposure during treatment were associated with more weight loss. About 20% of the patients were successful in reaching a clinically relevant weight loss,[20,30] with a mean weight reduction of more than 8 kg over 2 years. However, 16% of patients had relevant weight gain, and 2 years after anti−IL-5/5Ra treatment, approximately two-thirds of patients still had overweight or obesity. Thus, although anti−IL-5/5Ra−induced reduction of OCS exposure may have a beneficial effect on weight, this effect is small and not applicable to all patient groups, suggesting more issues to be addressed for patients with severe asthma who do not achieve weight loss but want to.

To our knowledge, this is the first study to investigate the long-term effects of anti−IL-5/5Ra treatment initiation on weight change in relation to OCS exposure. A previous report of 51 patients showed a significant reduction in BMI 6 months after starting anti−IL-5/5Ra biologics, although changes were minor.[24] In another US study, however, no significant changes in weight were observed after initiation of mepolizumab, benralizumab, or reslizumab, but again there were sample size limitations and a relatively short follow-up period (<1 year).[25] The mechanism explored in the present study relied on an anti−IL-5/5Ra−induced OCS reduction and subsequently possible weight loss, which requires a longer follow-up. Indeed, although the overall observed effect on weight in our study was small, we did see that the effect became more pronounced after 2 years of follow-up, especially in those patients with a history of higher OCS exposure. Our results suggest that anti−IL-5/5Ra−induced reduction in OCS exposure may contribute to weight loss, an outcome that will be welcomed by patients with severe asthma who would like to lose weight.

A strength of our study was the larger sample size and a longer follow-up period compared with previous literature, which allowed us to analyze the long-term effect of anti−IL-5/5Ra biologics on weight change in subgroups on the basis of OCS use. In addition, detailed data were available to assess OCS exposure from different perspectives (ie, maintenance OCS use and cumulative OCS dose 2 years before and 2 years after treatment initiation). This is an important contrast to other studies because data on cumulative OCS dose are rarely available, but highly relevant with regard to dose-dependent side effects.[7,8] The data on cumulative OCS dose allowed us to show that patients with higher OCS exposure before anti−IL-5/5Ra initiation and patients who managed to reduce their OCS exposure during anti−IL-5/5Ra treatment had higher weight loss 2 years after treatment initiation.

This study also has some limitations. Inherent to the design of our study, a control group of patients with severe eosinophilic asthma who are not on biologic treatment is lacking. To our knowledge, data on long-term weight changes in these patients are not available, but results from the placebo arm of phase 3 reslizumab trials suggest that no change in body weight occurs in the short-term.[25] Moreover, our study did not include any information on dietary intake or physical activity, which undoubtedly has an impact on a patient's weight. Yet, the mechanism explored in this study was related to (changes in) OCS exposure, and this information was accurately available, allowing us to demonstrate its relevance in weight change.

As hypothesized, we found more weight loss in patients with greater previous OCS exposure and greater anti−IL-5/5Ra−induced reduction in OCS use. This suggests that the hypothesized biological pathway of weight loss through OCS reduction seems plausible. Surprisingly, we did not see a higher BMI at baseline in the patients on maintenance OCS use.[5]

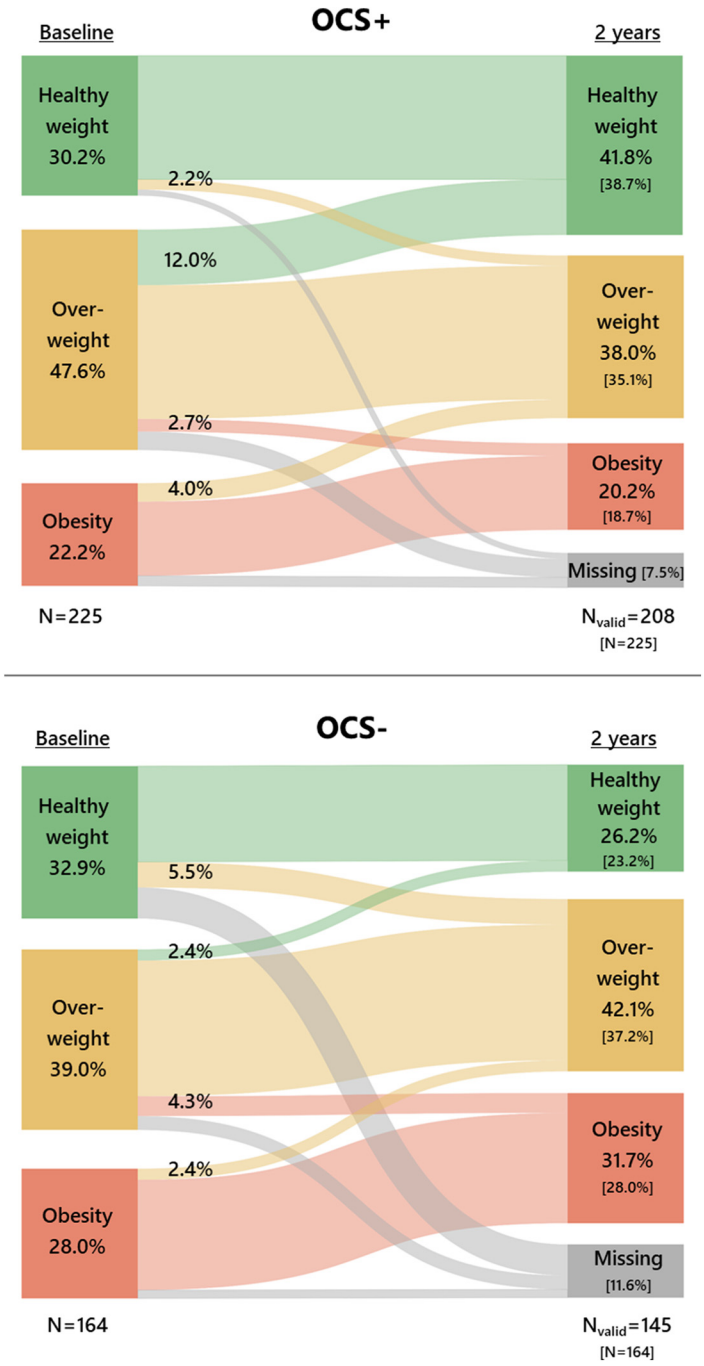

FIGURE 3. Change in BMI categories 2 years after anti—IL-5/5Ra initiation: BMI less than 25 kg/m^2 (*green*); BMI greater than or equal to 25 and less than 30 kg/m^2 (*yellow*); BMI greater than or equal to 30 kg/m^2 (*red*). *OCS+*, Patients with maintenance OCS use at anti—IL-5/5Ra initiation; *OCS−*, patients without maintenance OCS use at anti—IL-5/5Ra initiation. Percentage between brackets are based on total N equaling baseline N, including missing data.

Perhaps patients for whom maintenance OCS was unavoidable had already changed their diet or exercise habits to avoid the side effect of weight gain before starting anti—IL-5/5Ra treatment, and were able to further optimize this through better asthma control during the treatment. However, our registry has no information available on diet or exercise to support such an assumption. In line with previous findings,[24,25] a subgroup of our cohort gained weight during the follow-up period, which may be related to several lifestyle factors, but also an effect of reduced eosinophils as regulators of adipocyte homeostasis and body weight may not completely be ruled out, although this mechanism is still far from being understood.[31] Furthermore, it could be expected that patients with overweight or obesity have more room for improvement than patients with a healthy weight. Interestingly, no such effect was found in the sensitivity analysis in patients with a BMI greater than or equal to 25 kg/

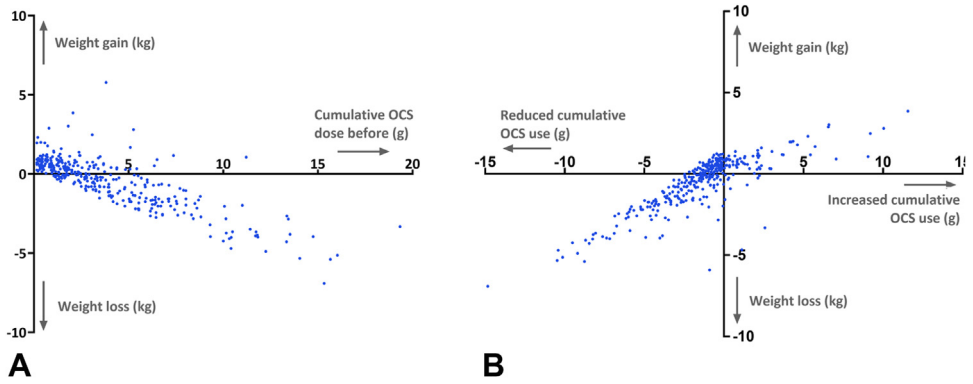

FIGURE 4. Weight change in relation to OCS exposure. (**A**) The association of weight change during 2-year follow-up and the cumulative OCS dose in the 2 years before anti−IL-5/5Ra initiation, and (**B**) the anti−IL-5/5Ra−induced change in cumulative OCS dose during the 2-year follow-up. Dots depict predicted values for weight change on the basis of an individual patient's age, sex, and smoking history, using linear regression.

m^2. This could be for many reasons: it is possible that the body composition of these patients changed, for example, because of increased activity, and fat mass was replaced by muscle mass, although this probably would not apply to many patients. Another explanation could be that BMI was an unintended proxy for an unmeasured confounder, such as lifestyle. Further stratification of this group into subgroups on the basis of maintenance OCS use at treatment initiation again suggested the important role of OCS exposure rather than BMI category at treatment initiation. Interestingly, a subgroup of patients gained weight in the 2 years after treatment initiation despite a reduction in OCS use (data not shown), suggesting that other mechanisms are involved in weight change in this subgroup that deserve more attention in clinical management.

The results of this study provide information for clinicians and will aid in managing the expectations of patients regarding weight changes after anti−IL-5/5Ra treatment initiation. Particularly in overweight patients with maintenance OCS use, an improvement in weight status can be expected. However, our results also show that 2 years after anti−IL-5/5Ra initiation, which is life-changing for many patients, approximately 65% of them are still not at a healthy weight. Although 20% of patients achieved a clinically relevant weight loss,[20,30] 16% of patients gained at least 5% of their baseline weight. Obviously, weight loss is a multifactorial process with complex interactions between behavior, lifestyle, and environment,[32] aspects that often receive little attention in our management of patients with severe asthma. If not done before, the start of biological therapy could be a very good marker to address these different aspects, for example, through referral to a lifestyle program, to elicit changes in patients with severe asthma for whom weight loss is desired and needed.

CONCLUSIONS

This real-world study in a large cohort of patients with severe eosinophilic asthma shows that anti−IL-5/5Ra therapy is associated with a significant reduction in weight over a 2-year period. The higher the OCS exposure before and the greater the OCS reduction during anti−IL-5/5Ra therapy, the more weight the patients lose. However, the observed effect is small and does not apply to all patient groups. Although a healthy weight is important to both the patient and the health care provider, most patients do not achieve this despite biological treatment, suggesting that additional interventions are needed if weight change is desired.

Acknowledgments

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TABLE E1. Overview of patients with clinically relevant weight loss and weight gain

Weight change parameters	N (%)
Total study population	353
Weight loss	69 (20)
Weight gain	56 (16)
BMI < 25 kg/m^2	108
Weight loss	11 (10)
Weight gain	20 (18)
BMI ≥ 25 and < 30 kg/m^2	157
Weight loss	38 (24)
Weight gain	22 (14)
BMI ≥ 30 kg/m^2	88
Weight loss	20 (23)
Weight gain	14 (16)

Absolute numbers and percentages are displayed. Weight loss: $\leq$5% of baseline weight after 2 y; weight gain: $\geq$5% of baseline weight after 2 y.

TABLE E2. Sensitivity analysis in patients with BMI ≥ 25 kg/m^2

Subgroup	β coefficient*	SE	95% CI	*P* value
BMI ≥ 25 kg/m^2	−0.07	0.16	−0.38 to 0.25	.67
BMI ≥ 25 kg/m^2 (OCS+)	−0.63	0.25	−1.12 to −0.15	.01
BMI ≥ 25 kg/m^2 (OCS−)	0.60	0.18	0.24 to 0.96	<.01

OCS+, Patients with maintenance OCS at anti−IL-5/5Ra initiation; *OCS−*, patients without maintenance OCS use at anti−IL-5/5Ra initiation.
*The β coefficient represents the mean change in kilograms per year for subgroups on the basis of BMI and maintenance OCS use groups.

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