




Cumulative corticosteroid-sparing effect of anti-interleukin-5/5Ra in eosinophilic asthma

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Shareable abstract (@ERSpublications)

Anti-IL-5/5Ra therapy leads to a reduction in cumulative oral corticosteroid exposure over a 2-year period. This study suggests that early anti-IL-5/5Ra intervention leads to a better long-term prognosis in patients with severe eosinophilic asthma. <https://bit.ly/3jzVGqW>

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Abstract

Background Anti-interleukin (IL)-5/IL-5 receptor α (IL-5Ra) therapy has been shown to reduce maintenance oral corticosteroid (OCS) dose in severe eosinophilic asthma. However, the effect on cumulative OCS exposure is currently unknown. Neither is it known how prior OCS exposure affects response to anti-IL-5/5Ra treatment. We aimed primarily to compare the cumulative OCS exposure over a 2-year period before and after anti-IL-5/5Ra initiation, and secondarily to investigate whether duration and cumulative OCS exposure prior to anti-IL-5/5Ra influence the ability to discontinue OCS within 2 years of anti-IL-5/5Ra therapy.

Methods This real-world nationwide observational registry-based study evaluated all dispensed OCS from 389 adults with severe eosinophilic asthma included in the Dutch Severe Asthma Registry (RAPSODI) 2 years before and 2 years after initiating anti-IL-5/5Ra. The Wilcoxon signed-rank test and multivariable regression analyses were used.

Results Median (interquartile range) cumulative OCS exposure in the 2 years before and after anti-IL-5/5Ra initiation decreased from 2.715 (1.150–5.539) to 1.050 (0.300–3.640) g ($p < 0.001$). 52% of patients were able to discontinue OCS within 2 years after anti-IL-5/5Ra therapy, which was independently predicted by lower and shorter prior OCS exposure.

Conclusions This real-world study showed that anti-IL-5/5Ra therapy leads to a significant reduction in cumulative OCS exposure over a 2-year period. Patients with lower and shorter OCS exposure were more likely to completely eliminate OCS. Since cumulative exposure increased progressively prior to anti-IL-5/5Ra initiation, our data suggest that early intervention leads to a better long-term prognosis in patients with severe eosinophilic asthma.

Introduction

Severe asthma is a debilitating form of asthma that is refractory to regular inhaled preventer therapy [1, 2]. The majority of patients with severe asthma present with an eosinophilic phenotype that is characterised by extensive eosinophilic inflammation in the airways [3], associated with ongoing asthma symptoms, poor quality of life, and severe and potentially fatal exacerbations that can only be controlled by recurrent or daily use of oral corticosteroids (OCS) [4–6]. Since its introduction in the early 1950s, the long-term use of systemic glucocorticoids is known to be associated with a multitude of serious adverse effects, including diabetes, cardiovascular disease and immunosuppression [7]. These comorbidities are associated with



increased morbidity and mortality rates, and high costs for society [8]. Studies have shown that OCS-related adverse effects are dose dependent and associated with the cumulative OCS exposure rather than the mean daily dose of OCS [9, 10].

After decades of unsuccessful searches for OCS-sparing treatments, a breakthrough has finally come in recent years with the availability of biologics, in particular biologics targeting interleukin (IL)-5, the major cytokine responsible for recruitment and activation of eosinophils [11]. Three biologics targeting the IL-5/IL-5 receptor α (IL-5Ra) pathway (mepolizumab, reslizumab and benralizumab) are currently approved for treatment of patients with severe eosinophilic asthma, resulting in significant reductions in the rate of severe asthma exacerbations and the daily maintenance dose of OCS [12–17].

Randomised controlled trials evaluating the effect of anti-IL-5/5Ra biologics on OCS use have evaluated the effect on the daily maintenance dose of OCS at 24–28 weeks [13, 16]. Recently, the PONENTE trial demonstrated the effectiveness of anti-IL-5Ra in safely reducing maintenance OCS using a personalised algorithm [18]. However, the cumulative OCS dose over a longer period before and after anti-IL-5/5Ra initiation is unknown. Also, the pattern and course of OCS exposure before starting anti-IL-5/5Ra treatment have never been explored. Finally, while the predictive value of mean baseline OCS dose on the response to anti-IL-5Ra has been previously established, it is not known whether the duration and extent of OCS use prior to biologic initiation influence the ability to completely eliminate the use of OCS [19]. Answering these questions is important, as it can help doctors predict whether biologics treatment will be effective for a particular severe asthma patient or not and it can inform patients what to expect from such treatment.

The present real-life study used patient data from the Dutch Registry of Adult Patients with Severe asthma for Optimal Disease management (RAPSODI), included between 1 December 2015 and 1 January 2019 with 2-year follow-up data. The primary aim of the study was to compare the cumulative exposure of OCS over a 2-year period prior to and after initiation of treatment with anti-IL-5/5Ra biologics for a nationwide population. Secondly, we studied the cumulative OCS exposure in patients with different durations of previous OCS use, and investigated whether the duration of previous OCS use and cumulative exposure predict the ability to stop OCS within 2 years after starting treatment with biologics.

Methods

Study design and patient population

This was a nationwide, multicentre observational registry-based real-world population study. The study population consisted of patients with severe asthma included in RAPSODI, which contains patient-level data on severe asthma patients from 19 Dutch hospitals. We selected and included all patients who initiated an anti-IL-5/5Ra biologic (mepolizumab, reslizumab or benralizumab) between 1 December 2015 and 1 January 2019, and who were followed for at least 24 months after initiation of this anti-IL-5/5Ra biologic. Inhaled medication doses and inhaler technique were optimised before initiating anti-IL-5/5Ra treatment, in concordance with the Dutch Severe Asthma Guidelines [20]. Patients were excluded if they were lost to follow-up or if they had inflammatory comorbidities (*e.g.* Crohn's disease and rheumatoid arthritis) to ensure that all OCS were prescribed for the treatment of severe asthma, preventing possible confounding. Informed consent for this study was collected at registry enrolment. A medical ethics committee approved the study. The study was registered in the Netherlands Trial Register (NL9041).

Measurements

Baseline characteristics at the moment of anti-IL-5/5Ra initiation were collected from the RAPSODI registry. Baseline data included: clinical characteristics (patient demographics, asthma duration, smoking history and year of anti-IL-5/5Ra initiation), surrogate inflammatory markers (peripheral blood eosinophils, exhaled nitric oxide fraction (F_{ENO})), receiving OCS maintenance treatment, OCS maintenance dose and number of exacerbations in the 12 months before anti-IL-5/5Ra initiation, lung function measurements (forced expiratory volume in 1 s (FEV_1)) and comorbidities (nasal polyposis and adrenal insufficiency).

In addition, dispensing data of systemic corticosteroids (Anatomical Therapeutic Chemical code H02AB) during the 24 months before and 24 months after anti-IL-5/5Ra initiation were requested from each patient's pharmacy. Dutch pharmacies have access to all dispensed medication for reasons of medication surveillance and reimbursement. To ensure that medication possibly dispensed at other pharmacies was captured, researchers made sure the patient consented to the Dutch National Exchange Point [21]. OCS exposure was expressed in prednisone-equivalent. In the Netherlands, medication is dispensed for a maximum period of 3 months; therefore, in addition to the total OCS exposure over 24 months, the cumulative OCS exposure was expressed in 3-month periods.

To study cumulative OCS exposure in patients with different durations of OCS use, patients were divided into three subgroups: 1) patients with first OCS dispensed ≤ 12 months before initiation of an anti-IL-5/5Ra biologic, 2) patients with first OCS dispensed >12 –21 months before initiation of an anti-IL-5/5Ra biologic and 3) patients with first OCS dispensed >21 months before initiation of an anti-IL-5/5Ra biologic. To investigate what proportion of patients was able to completely eliminate OCS after initiation of an anti-IL-5/5Ra biologic, patients were subdivided into two subgroups: those with and those without any OCS dispensed during the 18–24 months after initiating an anti-IL-5/5Ra biologic.

Statistical analysis

Continuous variables were expressed as median (interquartile range (IQR)) and categorical variables as percentages. Normality was assessed using the Kolmogorov–Smirnov test. The cumulative OCS exposures over the 24 months prior to and after initiating anti-IL-5/5Ra treatment were compared using the Wilcoxon signed-rank test. Bar charts were used to illustrate cumulative OCS exposure over 24 months and cumulative OCS exposures in 3-month periods in all patients, and in subgroups of patients with different duration of OCS exposure (≤ 12 , >12 –21 and >21 months). To visually compare the patterns of cumulative OCS use over time between these subgroups, we standardised the cumulative 3-month OCS doses to those of 100 patients.

The reduction of cumulative OCS exposure after initiating anti-IL-5/5Ra was calculated as percentage change from the exposure 0–3 months prior to anti-IL-5/5Ra initiation. OCS exposure after anti-IL-5/5Ra initiation was calculated per 3-month period and illustrated in a line chart.

To explore baseline variables associated with complete elimination of OCS within 2 years after anti-IL-5/5Ra initiation, binary logistic regression analysis was used. First, univariately associated factors ($p < 0.1$) were entered into a multivariable logistic regression model. Second, nonsignificant variables ($p \geq 0.05$) were removed using backward elimination. Factors independently associated with discontinuation of OCS within 2 years were expressed as odds ratios with 95% confidence intervals. In the analysis, the following contrasts were considered: blood eosinophils < 0.150 , ≥ 0.150 – 0.299 , ≥ 0.300 – 0.449 and $\geq 0.450 \times 10^9$ cells·L⁻¹; F_{ENO} < 25 , 25–49 and ≥ 50 ppb; pre-bronchodilator FEV₁ $< 80\%$ and $\geq 80\%$ predicted; start year of anti-IL-5/5Ra treatment 2015–2016, 2017 and 2018; first OCS exposure before anti-IL-5/5Ra ≤ 12 , >12 –21 and >21 months; and receiving OCS maintenance and without OCS maintenance before anti-IL-5/5Ra initiation. The cumulative OCS dose 2 years before anti-IL-5/5Ra was divided into quartiles ranging from lowest (quartile 1) to highest (quartile 4) OCS dose. The cumulative OCS dose 3 months before anti-IL-5/5Ra initiation was similarly analysed using quartiles.

All study-eligible patients in the registry were enrolled in the data analysis. Therefore no sample size calculation was performed.

A p-value < 0.05 indicated statistical significance. All statistical analyses were performed with SPSS Statistics version 26.0 (IBM, Armonk, NY, USA).

Results

Patients

Of the RAPSODI registry containing 878 patients on 1 January 2021, 462 patients initiated anti-IL-5/5Ra biologics (mepolizumab, reslizumab or benralizumab) before 1 January 2019 and were followed for ≥ 2 years. Data from 389 patients were used in the analysis (figure 1). The characteristics of included and excluded patients are compared in supplementary table S1. These groups did not differ. Table 1 shows the characteristics of the patients at anti-IL-5/5Ra initiation. Of note, 75.6% of the patients developed asthma as an adult, 42% were ex-smokers and 57.8% received maintenance OCS treatment. Information on comorbidities is demonstrated in supplementary table S2.

Change in cumulative OCS exposure

Overall cumulative OCS exposure standardised to 100 patients over the 24 months before and 24 months after initiating anti-IL-5/5Ra add-on treatment is illustrated in figure 2. The median (IQR) cumulative OCS dose in the 2 years before and after anti-IL-5/5Ra initiation decreased from 2.715 (1.150–5.539) to 1.050 (0.300–3.640) g ($p < 0.001$).

Figure 3 illustrates OCS exposure standardised to 100 patients for the 24 months before and 24 months after initiation of anti-IL-5/5Ra add-on therapy, expressed in dispensed prednisone-equivalent, per 3-month periods. In the years prior to initiating anti-IL-5/5Ra therapy, OCS exposure steadily increased. A rapid

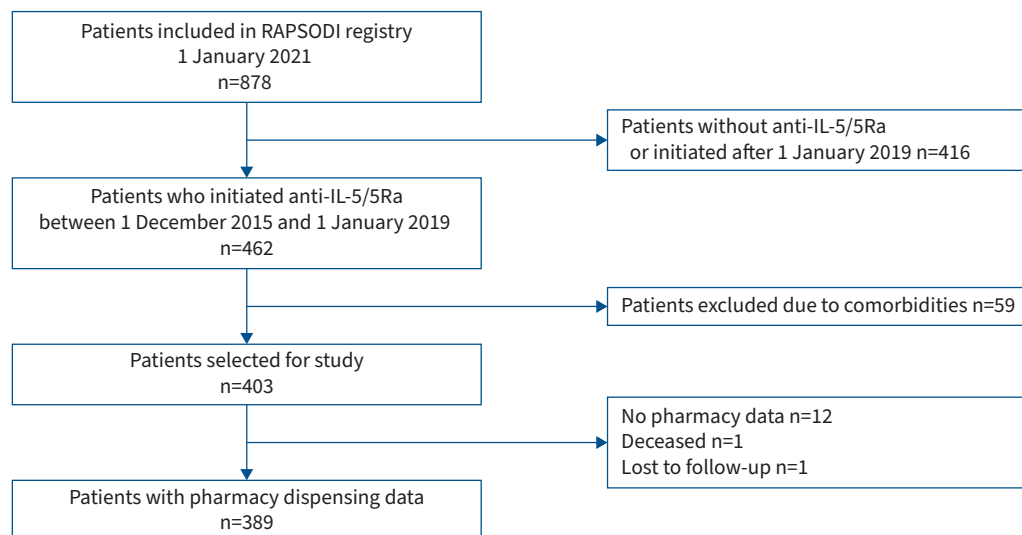


FIGURE 1 Flowchart of patient selection.

TABLE 1 Baseline patient characteristics (n=389)

Age (years)	57 (48–64)
Male	45.5
Body mass index (kg·m ⁻²)	27.3 (24.3–29.9)
Ex-smoker	42
Pack-years	10 (5–20)
Age of onset of eosinophilic asthma (years)	44 (23–53)
Late-onset asthma	75.6
Nonatopic asthma	53.4
Nasal polyposis	50.6
Adrenal insufficiency [#]	1.5
Exacerbations in previous year (n)	
0–1	23.4
2–5	56.1
>5	20.5
OCS maintenance	57.8
OCS maintenance dose (mg·day ⁻¹)	10 (6.3–15)
Blood eosinophils (×10 ⁹ L ⁻¹)	0.42 (0.20–0.67)
Blood eosinophil category (×10 ⁹ L ⁻¹)	
<0.150	20.6
≥0.150–0.299	13.6
≥0.300–0.449	18.7
≥0.450	47.1
F _{ENO} (ppb)	40 (24–76)
FEV ₁ (% pred)	76 (61–90.5)
Cumulative OCS 2 years before anti-IL-5/5Ra (g)	2.7 (1.2–5.5)
Cumulative OCS 3 months before anti-IL-5/5Ra (g)	0.45 (0.013–0.90)
Start year of anti-IL-5/5Ra therapy	
2015–2016	28.3
2017	33.7
2018	38.0
First OCS exposure before anti-IL-5/5Ra therapy	
≤12 months	16.7
>12–21 months	28.0
>21 months	55.3

Data are presented as median (interquartile range) or %. OCS: oral corticosteroids (prednisone-equivalent); F_{ENO}: exhaled nitric oxide fraction; FEV₁: forced expiratory volume in 1 s; IL-5: interleukin-5; IL-5Ra: IL-5 receptor α .
#: underreported in this study.

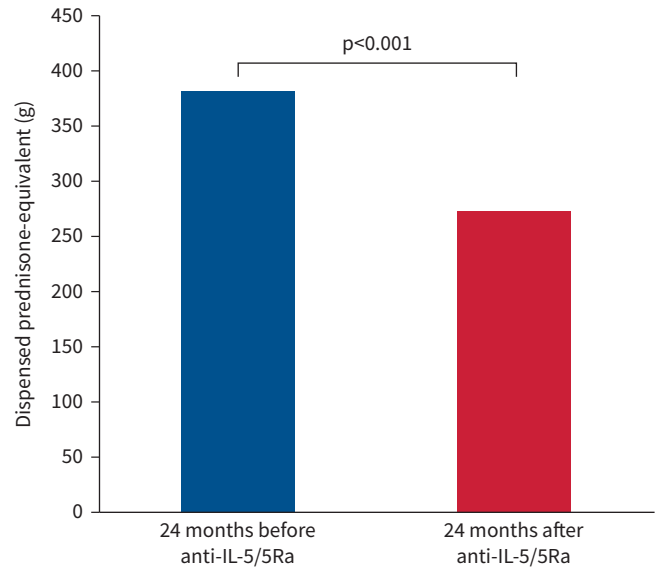


FIGURE 2 Cumulative oral corticosteroid exposure standardised to 100 patients (n=389) expressed in dispensed prednisolone-equivalent over the 24 months before and after anti-interleukin (IL)-5/IL-5 receptor α (IL-5Ra) initiation. The exposure decreased significantly ($p < 0.001$).

and significant reduction of OCS exposure was observed after initiating anti-IL-5/5Ra therapy, but OCS exposure was not eliminated in all patients.

Figure 4a–c illustrates OCS exposure for the 24 months before and 24 months after initiation of anti-IL-5/5Ra add-on therapy, expressed as dispensed prednisone-equivalent, per 3-month periods in three subgroups with different OCS exposure times: ≤ 12 , >12 –21 and >21 months before initiation of an anti-IL-5/5Ra biologic. OCS exposures were standardised to groups of 100 patients for reasons of comparability between groups. The data show that the longer the period of OCS exposure, the higher the 3-month cumulative

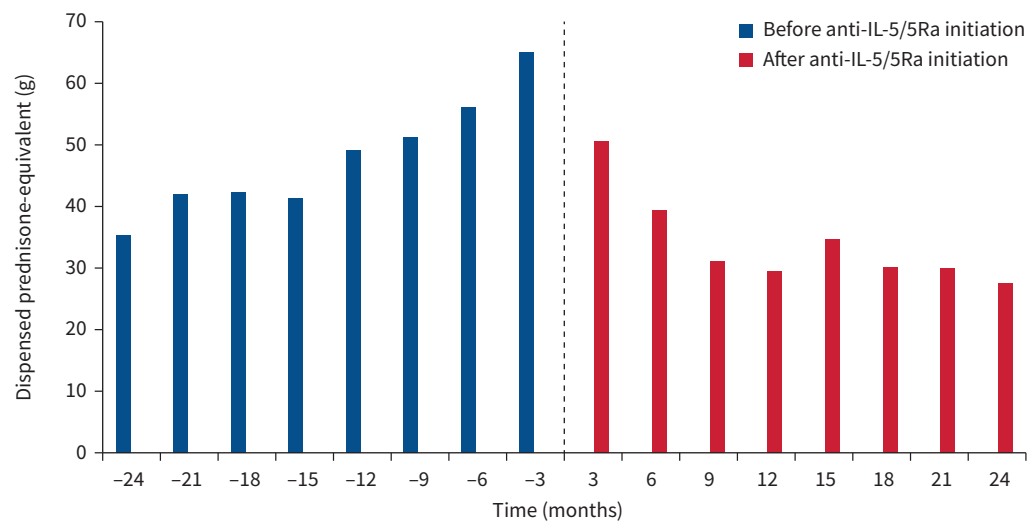


FIGURE 3 Cumulative oral corticosteroid (OCS) exposure in dispensed prednisolone-equivalent 24 months before and after initiating anti-interleukin (IL)-5/IL-5 receptor α (IL-5Ra) (dotted line), expressed per 3 months, standardised to 100 patients (n=389). Over the 24 months before anti-IL-5/5Ra initiation, the OCS dose per 3 months increased by 84%. An OCS maintenance dose of $5 \text{ mg}\cdot\text{day}^{-1}$ equals 0.45 g per 3 months; a 7-day OCS course equals 0.21 g.

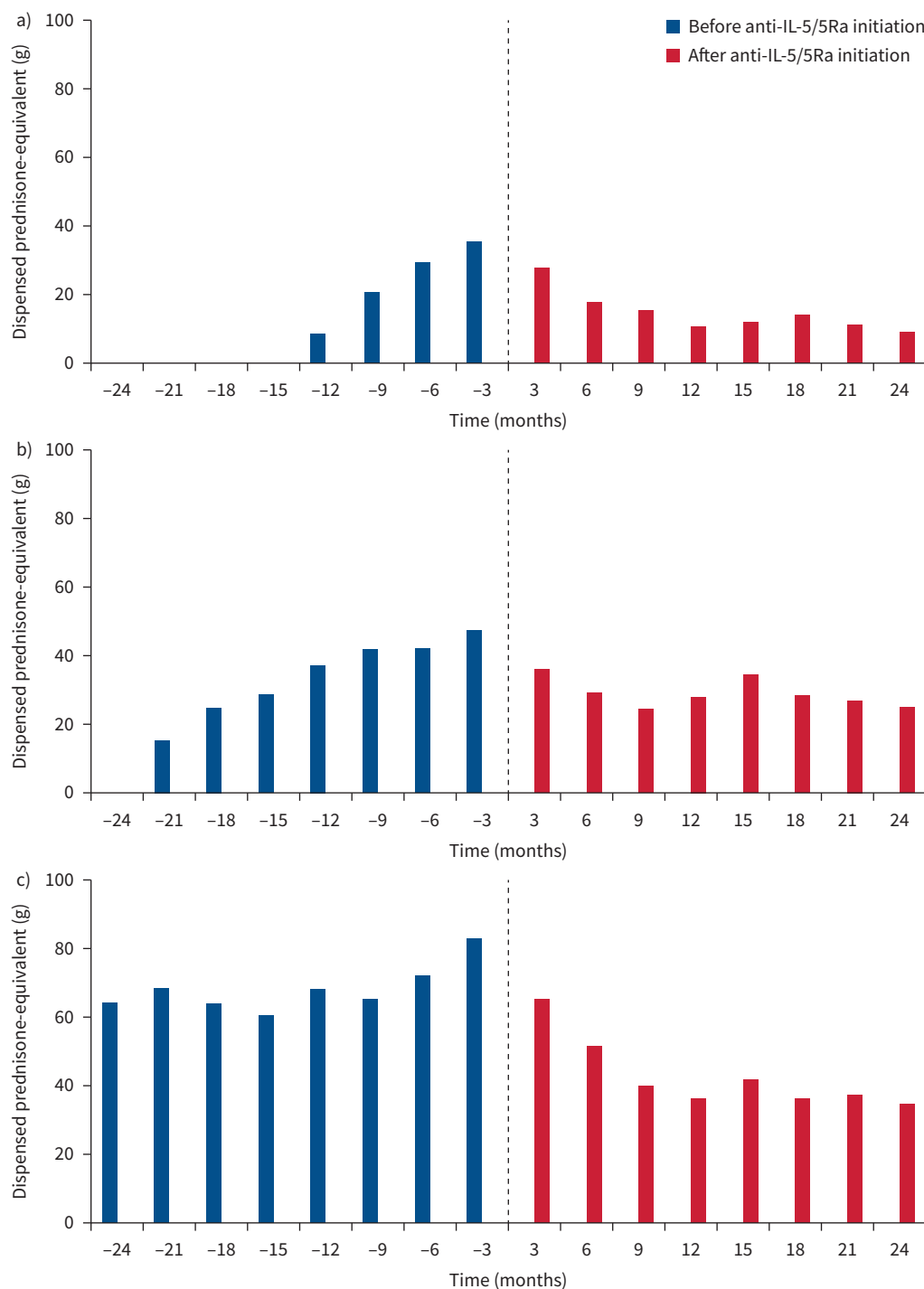


FIGURE 4 Cumulative oral corticosteroid (OCS) exposure in dispensed prednisolone-equivalent 24 months before and after initiating anti-interleukin (IL)-5/IL-5 receptor α (IL-5Ra) (dotted line), expressed per 3 months, standardised to 100 patients: patients with first OCS exposure a) ≤ 12 months (n=65), b) >12 –21 months (n=109) and c) >21 months (n=215) before anti-IL-5/5Ra.

OCS exposure. In addition, the data also show that the longer and higher the exposure before initiation of anti-IL-5/5Ra therapy, the higher the cumulative OCS use after 2 years of anti-IL-5/5Ra therapy. The proportion of patients requiring OCS dispensing after initiating anti-IL-5/5Ra, subdivided in duration subgroups, is displayed in supplementary figure S1.

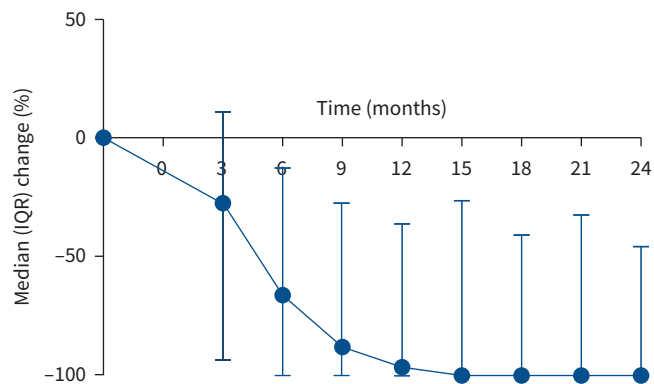


FIGURE 5 Change in oral corticosteroid exposure after anti-interleukin (IL)-5/IL-5 receptor α (IL-5Ra) initiation (T=0), per 3 months, compared with 3 months before anti-IL-5/5Ra (n=389).

Ability to stop OCS after initiating anti-IL-5/5Ra therapy

Figure 5 shows the median change in cumulative OCS dose after anti-IL-5/5Ra initiation compared with the 3 months before anti-IL-5/5Ra initiation. At 6 months after anti-IL-5/5Ra initiation, the median (IQR) OCS exposure per 3-month period was reduced to 0.126 (0–0.591) g, a reduction of 66% compared with the 3-month period before initiation of anti-IL-5/5Ra ($p<0.001$). Beyond 6 months, the median reduction continued and reached 100% after 15 months. 52% of the population (202 patients) were able to discontinue OCS within 2 years of anti-IL-5/5Ra therapy. The baseline median (IQR) OCS maintenance dose did not differ between patients able or unable to discontinue OCS within 2 years of anti-IL-5/5Ra treatment (10 (7.5–15) versus 10 (5–11.3) mg·day⁻¹; $p=0.132$).

Predictors of ability to stop OCS use

Univariate and multivariable significant predictors of OCS discontinuation within 2 years are described in table 2. All variables that were examined are described in supplementary table S3. Three variables independently predicted the ability of OCS discontinuation: 1) lower total OCS exposure over the 24 months before anti-IL-5/5Ra initiation, 2) shorter duration of OCS exposure and 3) later year of starting anti-IL-5/5Ra therapy.

Discussion

This real-world study shows that anti-IL-5/5Ra add-on treatment for severe eosinophilic asthma leads to a significant reduction in cumulative OCS exposure in the majority of patients. Furthermore, OCS exposure increases progressively in the years prior to anti-IL-5/5Ra initiation and declines rapidly after initiating anti-IL-5/5Ra therapy. More than half of the patients are able to completely eliminate OCS within 2 years of initiating anti-IL-5/5Ra therapy. This is especially true for patients with shorter OCS exposure and lower cumulative OCS doses, suggesting that early introduction of anti-IL-5/5Ra therapy leads to better therapeutic results.

The results of our study confirm and are an important extension of previous findings from controlled trials and real-world studies with anti-IL-5/5Ra biologics. Most placebo-controlled studies focused on the daily OCS maintenance dose and found ~50% dose reduction relative to placebo after 24 weeks of treatment with anti-IL-5/5Ra biologics, which is comparable to the findings in our study [13, 16]. However, unlike our study, these studies did not examine the effect on cumulative OCS dose, which is a better predictor of OCS-related side-effects than the daily dose at some point in the disease [9]. Our findings regarding discontinuation of OCS after initiation of anti-IL-5/5Ra were also observed in three other studies. The recently published PONENTE study provided detailed information on how to safely reduce OCS after initiation of anti-IL-5Ra using a personalised OCS reduction algorithm. In the PONENTE study, the majority of patients were able to eliminate OCS and nearly all patients achieved a daily maintenance dose of ≤ 5 mg·day⁻¹ [18]. An Australian real-world study examining the effect of mepolizumab in 309 patients found a reduction in the proportion of patients requiring OCS (maintenance and/or bursts) from 97% to 67% after 12 months of treatment [22]. Yet another study, based on insurance claims in the USA including 527 patients, found an increase in the proportion of patients without OCS use from 6.6% to 20.3% after 12 months of mepolizumab treatment [23]. Our study included a longer observation period of 2 years before and 2 years after initiation of anti-IL-5/5Ra therapy, which allowed us not only to calculate

TABLE 2 Significant factors associated with complete elimination of oral corticosteroids (OCS) after 2 years of anti-interleukin (IL)-5/IL-5 receptor α (IL-5Ra)

	Univariate analysis		Multivariable analysis	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Cumulative OCS dose during 2 years before anti-IL-5/5Ra therapy		<0.001		<0.001
Quartile 1 (≤ 1.1 g)	1		1	
Quartile 2 (>1.1–2.7 g)	0.4 (0.22–0.75)	0.004	0.45 (0.23–0.88)	0.02
Quartile 3 (>2.7–5.5 g)	0.25 (0.13–0.46)	<0.001	0.27 (0.13–0.53)	<0.001
Quartile 4 (≥ 5.6 g)	0.11 (0.06–0.21)	<0.001	0.11 (0.052–0.24)	<0.001
First OCS exposure before anti-IL-5/5Ra therapy		<0.001		0.018
≤ 12 months	1		1	
>12–21 months	0.3 (0.15–0.59)	<0.001	0.42 (0.20–0.88)	0.022
>21 months	0.29 (0.16–0.54)	<0.001	0.83 (0.40–1.7)	0.62
Starting year of anti-IL-5/5Ra therapy		<0.001		0.004
2015–2016	1		1	
2017	1.8 (1.1–3.0)	0.032	1.7 (0.99–3.1)	0.056
2018	2.9 (1.8–4.9)	<0.001	2.6 (1.5–4.5)	<0.001
OCS maintenance therapy prior to anti-IL-5/5Ra therapy				
Yes	0.37 (0.25–0.57)	<0.001		NS
FEV₁ (% pred)				
Continuous	0.99 (0.98–1.0)	0.052		NS
FEV₁ (% pred)				
$\geq 80\%$	0.7 (0.46–1.1)	0.088		NS
F_{ENO} (ppb)				
Continuous	1.006 (1.000–1.011)	0.045		NS
F_{ENO} (ppb)		0.094		NS
<25	1			
25–49	0.89 (0.48–1.7)	0.70		
≥ 50	1.6 (0.89–2.8)	0.12		
OCS dose during 3 months prior to anti-IL-5/5Ra therapy		<0.001		NS
Quartile 1 (≤ 0.03 g)	1			
Quartile 2 (0.04–0.45 g)	0.55 (0.30–0.98)	0.044		
Quartile 3 (>0.45–0.90 g)	0.4 (0.22–0.72)	0.002		
Quartile 4 (≥ 0.91 g)	0.21 (0.11–0.39)	<0.001		
Blood eosinophil category ($\times 10^9$ L⁻¹)		0.023		NS
<0.150	1			
≥ 0.150 –0.299	1.5 (0.72–3.1)	0.284		
≥ 0.300 –0.449	2.2 (1.1–4.2)	0.025		
≥ 0.450	2.3 (1.3–4.0)	0.003		

F_{ENO}: exhaled nitric oxide fraction; FEV₁: forced expiratory volume in 1 s; ns: nonsignificant in backward stepwise regression analysis.

cumulative OCS exposure, but also to determine the course of OCS exposure before and after starting anti-IL-5/5Ra therapy, and to demonstrate that longer duration and higher total exposure to OCS predicted a poorer response to anti-IL-5/5Ra therapy.

Our large nationwide study is unique in that it provides insight into the use of OCS for 2 years prior to initiation of anti-IL-5/5Ra treatment. To the best of our knowledge, this has never been done before and provides important information about the course of severe eosinophilic asthma. Data on OCS use were collected by directly contacting the patients' pharmacies. Dutch pharmacies have access to all dispensed medication for reasons of medication surveillance and reimbursement. The Dutch National Exchange Point prevented medication dispensed at other pharmacies during the study period being missed in the analysis. This guaranteed a complete overview of the OCS exposure and prevented possible recall bias. While randomised controlled trials and subsequent real-world studies only evaluated the effect of anti-IL-5/5Ra biologics on the daily maintenance dose of OCS, in our study we could accurately calculate the cumulative OCS exposure over several years. This will allow a better estimate of the effect

of anti-IL-5/5Ra on the long-term adverse effects of OCS that are primarily related to the cumulative OCS exposure.

Our study has some limitations as well. First, there are the usual limitations inherent of a real-world intervention study, *e.g.* the lack of a control group. The registry did not allow for a control group, since patients without a biologic were not included and the numbers of patients first starting a non-anti-IL-5/5Ra biologic were limited. A second limitation of this study is that dispensing medication does not imply that the patient actually takes the medication. Due to the retrospective character of our study, it was not possible to verify that the medication was taken as prescribed. However, given the severity of the disease and the eventual dependence on OCS, it seems likely that all medications were used. Third, we did not have access to data on systemic corticosteroid use during hospital admissions. However, as this may have led to an underestimation of OCS use, especially in the pre-initiation period of anti-IL-5/5Ra therapy, this would only further augment the effects found in our study. Furthermore, our selection of patients might have influenced the observed progression prior to anti-IL-5/5Ra initiation because patients with OCS progression might be more likely to be deemed anti-IL-5/5Ra eligible. On the other hand, the reduction in OCS exposure might have been influenced by so-called regression to the mean due to the possible selection of patients initiating anti-IL-5/5Ra therapy at a time when they experienced more severe symptoms, which would also have spontaneously improved after starting therapy. Although unlikely given the prolonged pre-treatment observation period, we cannot fully exclude this possibility.

We found a progressive course of OCS exposure in the 2 years before anti-IL-5/5Ra initiation, which was especially evident in patients with relatively short OCS exposure. This suggests that severe eosinophilic asthma, which is known to usually start in adulthood, has a progressive course in the first years with a rapid increase in the need for OCS. Such a rapidly progressive disease course might be related to the formation of immunogenic Charcot–Leyden crystals, the activation of airway autoantibodies or the autocrine production of IL-5/5Ra by eosinophilic granulocytes leading to a self-reinforcing inflammation requiring treatment with ever higher doses of OCS [24–26]. If future studies confirm the progressive course of eosinophilic asthma, this will have a major impact on the management of this severe condition.

We showed that the ability to completely eliminate the use of OCS within 2 years after anti-IL-5/5Ra initiation is associated with lower and shorter OCS exposure before initiating anti-IL-5/5Ra, which is not surprising. But how to explain that a later start year of anti-IL-5/5Ra therapy influenced the ability to eliminate OCS? The most likely explanation is that the first patients prescribed anti-IL-5/5Ra therapy were those with the most severe illness and highest OCS exposure, who had waited the longest time for health authorities to approve this add-on therapy. In later years, anti-IL-5/5Ra treatment became more accessible to patients with milder disease and lower OCS exposure, which may be an explanation why the effect of treatment was greater in those patients and why they could more easily discontinue OCS altogether. The suggestion that initially patients with more severe asthma were included could also be inferred from their baseline characteristics showing that nearly 58% used maintenance OCS, 42% were ex-smokers and 50.6% were diagnosed with nasal polyposis. These numbers are higher compared with patients in the US Severe Asthma Research Program (SARP III) and European Unbiased Biomarkers for the Prediction of Respiratory Disease Outcomes (U-BIOPRED) cohorts [27, 28]. Therefore, it would be interesting to make a comparison with other severe asthma cohorts in order to better estimate the generalisability of our findings.

Our study showed that even after 2 years of anti-IL-5/5Ra therapy only half of our patients were able to discontinue the use of OCS. This can have several explanations. For example, there may still be active airway inflammation, which cannot be completely suppressed by anti-IL-5/5Ra. Possible contributing factors are an inadequate serum concentration or insufficient tissue concentration of anti-IL-5/5Ra, or involvement of another pathophysiological pathway in the inflammatory process, *e.g.* the IL-4/IL-13 pathway [29, 30]. Another possible explanation for the residual OCS exposure is adrenal insufficiency, which is a major side-effect of long-term OCS use [31]. Adrenal insufficiency was not systematically assessed in the study population, which has likely led to an underreporting of adrenal insufficiency. The recent PONENTE trial found that 60% of patients had any form of adrenal insufficiency at the time treatment with the anti-IL-5Ra biologic benralizumab was initiated [18]. Studies like the PONENTE trial show that adrenal insufficiency is underrecognised in the Dutch severe asthma population. The need to systematically examine adrenal insufficiency has been highlighted by the PONENTE trial and should lead to a major change in current clinical practice. Estimates about the influence of the duration and extent of OCS exposure on the occurrence of adrenal insufficiency are currently lacking. This remains a topic for future studies in patients with severe eosinophilic asthma.

An important clinical implication of our findings is that physicians treating patients with severe eosinophilic asthma should consider initiating anti-IL-5/5Ra treatment early in the disease process, when their patients require relatively low doses of OCS to control their asthma. Furthermore, clinicians and patients should be aware of possible residual OCS exposure despite anti-IL-5/5Ra treatment and pursue further treatment optimisation either through individualised OCS taper schedules as suggested in the PONENTE study or by switching to add-on therapies targeting different inflammatory pathways. Furthermore, due to the observed progressive course of the OCS dose, our results indicate that there is an unmet need to obtain more insight into the natural course of severe eosinophilic asthma.

In conclusion, this real-world study showed that anti-IL-5/5Ra therapy leads to a significant reduction in cumulative OCS exposure over a 2-year period. Patients who develop severe eosinophilic asthma appear to have a rapid progression of cumulative OCS exposure associated with an increased risk of adverse events. The lower and shorter the OCS exposure, the more patients might benefit from anti-IL-5/5Ra add-on treatment and achieve complete elimination of OCS use. These data suggest that early intervention with anti-IL-5/5Ra biologics in patients with severe eosinophilic asthma leads to a better long-term prognosis.

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This study is registered at the Netherlands Trial Register with identifier NL9041.

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