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

**Johannes A. Kroes[1,2], Sybrand W.J. Zielhuis[2], Kim De Jong[3], Simone Hashimoto[4], Jacob K. Sont[5], Sander W. Zielhuis[1], Eric N. Van Roon[1,2], Elisabeth H. Bel[4] and Anneke Ten Brinke[6] on behalf of the RAPSODI Team**

[1]Dept of Clinical Pharmacy and Pharmacology, Medical Centre Leeuwarden, Leeuwarden, The Netherlands. [2]Unit of Pharmacotherapy, Epidemiology and Economics, Dept of Pharmacy, University of Groningen, Groningen, The Netherlands. [3]Dept of Epidemiology, Medical Centre Leeuwarden, Leeuwarden, The Netherlands. [4]Dept of Respiratory Medicine, Amsterdam University Medical Centres, University of Amsterdam, Amsterdam, The Netherlands. [5]Medical Decision Making, Dept of Biomedical Data Sciences, Leiden University Medical Centre, Leiden, The Netherlands. [6]Dept of Pulmonology, Medical Centre Leeuwarden, Leeuwarden, The Netherlands.

Corresponding author: Johannes A. Kroes (j.a.kroes@rug.nl)

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

**Cite this article as:** Kroes JA, Zielhuis SWJ, De Jong K, *et al*. Cumulative corticosteroid-sparing effect of anti-interleukin-5/5Ra in eosinophilic asthma. *Eur Respir J* 2022; 60: 2102983 [DOI: 10.1183/13993003.02983-2021].



This article has an editorial commentary: https://doi.org/10.1183/13993003.01440-2022

Received: 20 Nov 2021
Accepted: 31 March 2022

## 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. Secondarily, 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 ($p\geqslant0.05$) 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 ⩾0.450×$10^9$ cells·$L^{-1}$; $F_{ENO}$ <25, 25–49 and ⩾50 ppb; pre-bronchodilator $FEV_1$ <80% and ⩾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

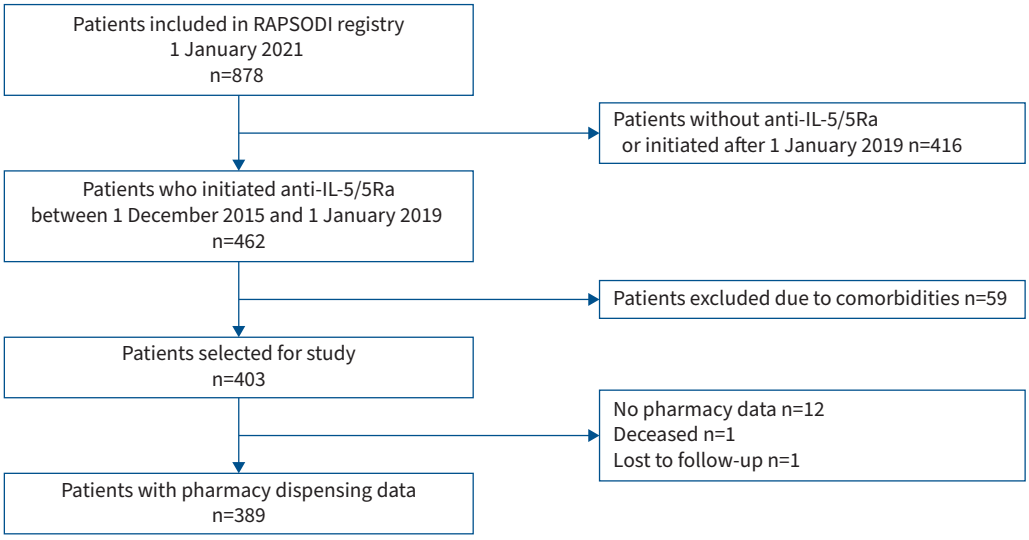


**FIGURE 1** Flowchart of patient selection.

**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; FEV$_1$: forced expiratory volume in 1 s; IL-5: interleukin-5; IL-5Ra: IL-5 receptor α. [#]: underreported in this study.

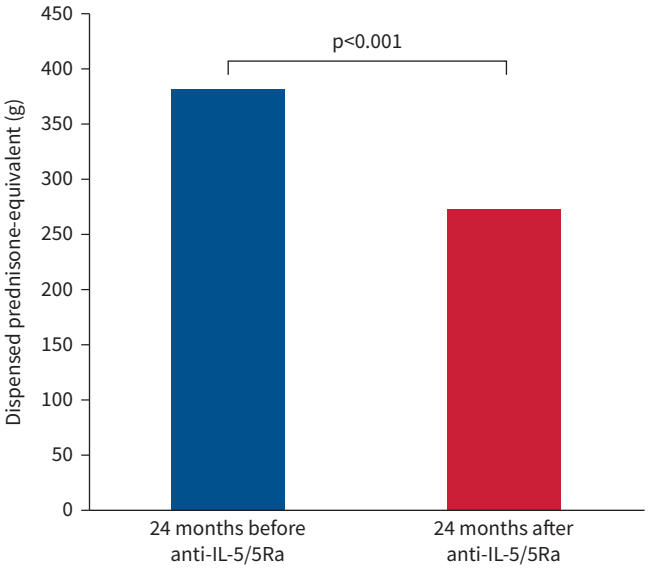


**FIGURE 2** Cumulative oral corticosteroid exposure standardised to 100 patients (n=389) expressed in dispensed prednisolone-equivalent over the 24 months before and after anti-interleukin (IL)-5/IL-5 receptor α (IL-5Ra) initiation. The exposure decreased significantly (p<0.001).

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

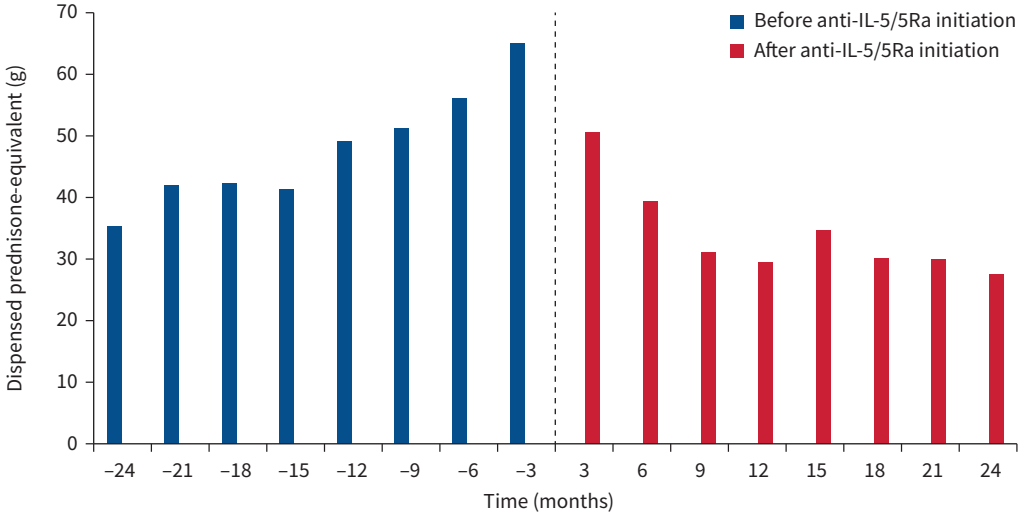


**FIGURE 3** Cumulative oral corticosteroid (OCS) exposure in dispensed prednisolone-equivalent 24 months before and after initiating anti-interleukin (IL)-5/IL-5 receptor α (IL-5Ra) (dotted line), expressed per 3 months, standardised to 100 patients (n=389). Over the 24 months before anti-IL-5/5Ra initiation,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

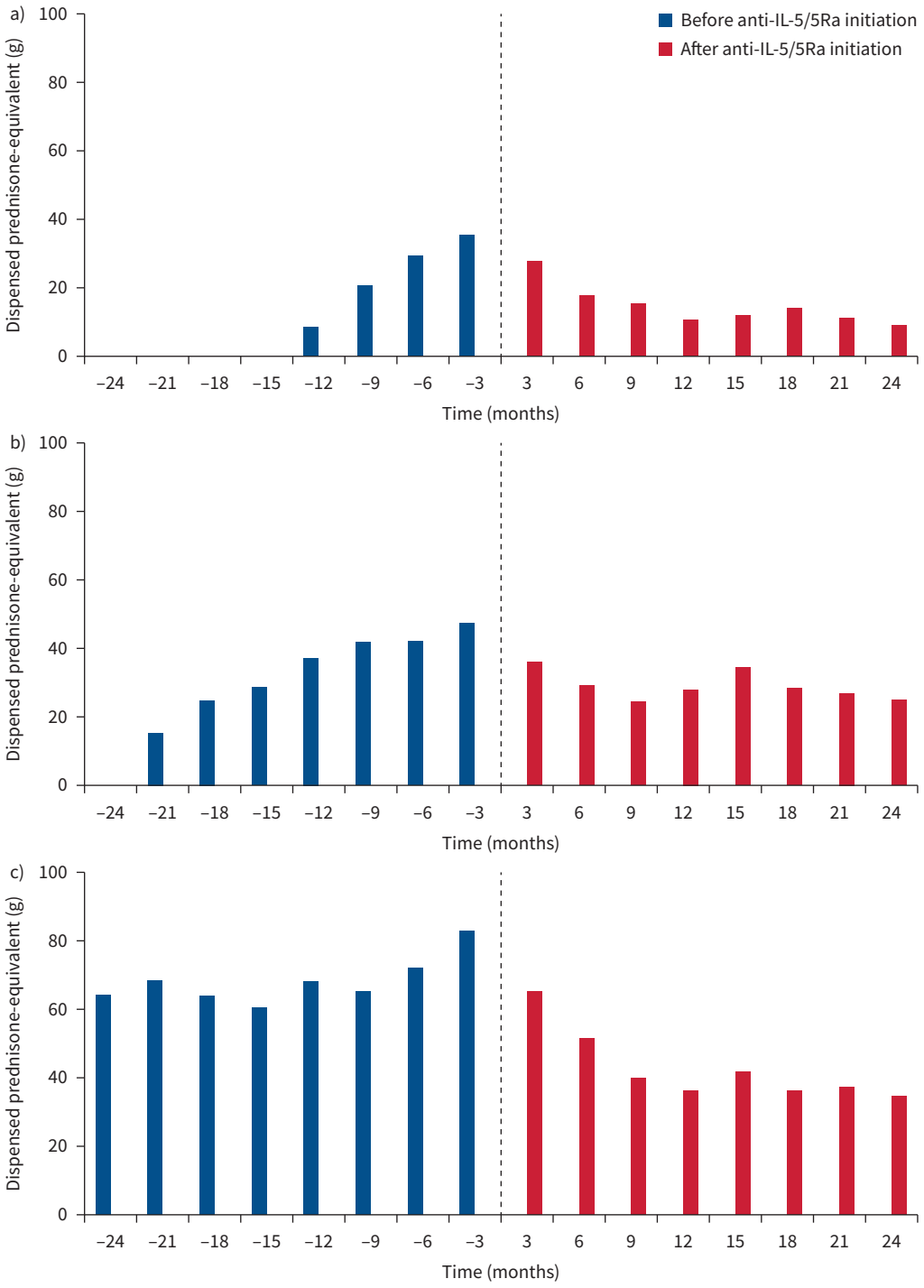


**FIGURE 4** Cumulative oral corticosteroid (OCS) exposure in dispensed prednisolone-equivalent 24 months before and after initiating anti-interleukin (IL)-5/IL-5 receptor α (IL-5Ra) (dotted line), expressed per 3 months, standardised to 100 patients: patients with first OCS exposure a) ⩽12 months (n=65),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

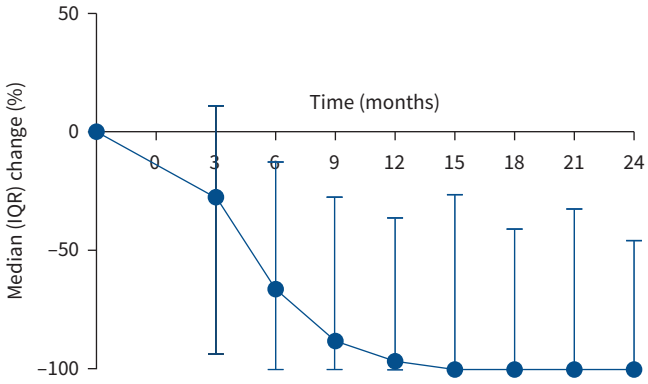


**FIGURE 5** Change in oral corticosteroid exposure after anti-interleukin (IL)-5/IL-5 receptor α (IL-5Ra) initiation (T=0), per 3 months, compared with 3 months before anti-IL-5/5Ra (n=389).

### *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) $mg \cdot day^{-1}$; 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 $\leqslant 5$ $mg \cdot day^{-1}$ [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 |
| **$FEV_1$ (% pred)** | | | | |
| Continuous | 0.99 (0.98–1.0) | 0.052 | | NS |
| **$FEV_1$ (% pred)** | | | | |
| ⩾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; $FEV_1$: 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.

Acknowledgements: The authors would like to thank Nic Veeger (Dept of Epidemiology, Medical Centre Leeuwarden, Leeuwarden, The Netherlands) for his contribution to the statistical analysis. This study was conducted on behalf of the Dutch Registry of Adult Patients with Severe asthma for Optimal DIsease management (RAPSODI) (a full acknowledgement list is provided in the supplementary material).

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

Conflict of interest: J.A. Kroes reports a grant from AstraZeneca, unrelated to this work. S.W.J. Zielhuis has nothing to disclose. K. De Jong has nothing to disclose. S. Hashimoto has nothing to disclose. J.K. Sont reports a grant from AstraZeneca, unrelated to this work. S.W. Zielhuis reports a grant from AstraZeneca and personal fees from Novartis, GlaxoSmithKline, Sanofi-Genzyme Regeneron, Eli-Lilly and Merck Sharp & Dohme, unrelated to this work. E.N. Van Roon has nothing to disclose. E.H. Bel reports grants from GlaxoSmithKline and Teva, and personal fees from GlaxoSmithKline, Teva, AstraZeneca, Sanofi-Genzyme Regeneron, Chiesi and Sterna, unrelated to this work. A. Ten Brinke reports grants from AstraZeneca, GlaxoSmithKline, Teva and Sanofi-Genzyme Regeneron, and personal fees from GlaxoSmithKline, Teva, AstraZeneca and Sanofi-Genzyme Regeneron, unrelated to this work.

Support statement: The Registry of Adult Patients with Severe asthma for Optimal DIsease management (RAPSODI) is financially supported by an unrestricted grant from GlaxoSmithKline, Novartis Pharma, AstraZeneca, Teva and Sanofi-Genzyme Regeneron.

## References

1 Global Initiative for Asthma (GINA). Difficult-to-treat & Severe Asthma in Adolescent and Adult Patients. Diagnosis and Management. 2021. www.ginasthma.org/wp-content/uploads/2021/08/SA-Pocket-guide-v3.0-SCREEN-WMS.pdf Date last accessed: 13 September 2021.
2 Holguin F, Cardet JC, Chung KF, *et al.* Management of severe asthma: a European Respiratory Society/American Thoracic Society guideline. *Eur Respir J* 2019; 55: 1900588.
3 Heaney LG, Perez de Llano L, Al-Ahmad M, *et al.* Eosinophilic and noneosinophilic asthma: an expert consensus framework to characterize phenotypes in a global real-life severe asthma cohort. *Chest* 2021; 160: 814–830.
4 Pizzichini MM, Pizzichini E, Clelland L, *et al.* Prednisone-dependent asthma: inflammatory indices in induced sputum. *Eur Respir J* 1999; 13: 15–21.
5 Sousa AR, Marshall RP, Warnock LC, *et al.* Responsiveness to oral prednisolone in severe asthma is related to the degree of eosinophilic airway inflammation. *Clin Exp Allergy* 2017; 47: 890–899.
6 van Bragt JJMH, Adcock IM, Bel EHD, *et al.* Characteristics and treatment regimens across ERS SHARP severe asthma registries. *Eur Respir J* 2020; 55: 1901163.
7 Bleecker ER, Menzies-Gow AN, Price DB, *et al.* Systematic literature review of systemic corticosteroid use for asthma management. *Am J Respir Crit Care Med* 2020; 201: 276–293.
8 Voorham J, Xu X, Price DB, *et al.* Healthcare resource utilization and costs associated with incremental systemic corticosteroid exposure in asthma. *Allergy* 2019; 74: 273–283.
9 Dalal AA, Duh MS, Gozalo L, *et al.* Dose-response relationship between long-term systemic corticosteroid use and related complications in patients with severe asthma. *J Manag Care Spec Pharm* 2016; 22: 833–847.
10 Walsh LJ, Wong CA, Oborne J, *et al.* Adverse effects of oral corticosteroids in relation to dose in patients with lung disease. *Thorax* 2001; 56: 279–284.

11 Hilvering B, Xue L, Pavord ID. Evidence for the efficacy and safety of anti-interleukin-5 treatment in the management of refractory eosinophilic asthma. *Ther Adv Respir Dis* 2015; 9: 135–145.
12 Ortega HG, Liu MC, Pavord ID, *et al.* Mepolizumab treatment in patients with severe eosinophilic asthma. *N Engl J Med* 2014; 371: 1198–1207.
13 Bel EH, Wenzel SE, Thompson PJ, *et al.* Oral glucocorticoid-sparing effect of mepolizumab in eosinophilic asthma. *N Engl J Med* 2014; 371: 1189–1197.
14 Castro M, Zangrilli J, Wechsler ME, *et al.* Reslizumab for inadequately controlled asthma with elevated blood eosinophil counts: results from two multicentre, parallel, double-blind, randomised, placebo-controlled, phase 3 trials. *Lancet Respir Med* 2015; 3: 355–366.
15 Nair P, Bardin P, Humbert M, *et al.* Efficacy of intravenous reslizumab in oral corticosteroid-dependent asthma. *J Allergy Clin Immunol Pract* 2020; 8: 555–564.
16 Nair P, Wenzel S, Rabe KF, *et al.* Oral glucocorticoid-sparing effect of benralizumab in severe asthma. *N Engl J Med* 2017; 376: 2448–2458.
17 Bleecker ER, FitzGerald JM, Chanez P, *et al.* Efficacy and safety of benralizumab for patients with severe asthma uncontrolled with high-dosage inhaled corticosteroids and long-acting β-agonists (SIROCCO): a randomised, multicentre, placebo-controlled phase 3 trial. *Lancet* 2016; 388: 2115–2127.
18 Menzies-Gow A, Gurnell M, Heaney LG, *et al.* Oral corticosteroid elimination *via* a personalised reduction algorithm in adults with severe, eosinophilic asthma treated with benralizumab (PONENTE): a multicentre, open-label, single-arm study. *Lancet Respir Med* 2022; 10: 47–58.
19 Bleecker ER, Wechsler ME, FitzGerald JM, *et al.* Baseline patient factors impact on the clinical efficacy of benralizumab for severe asthma. *Eur Respir J* 2018; 52: 1800936.
20 NVALT. Aanvullende behandelingen bij ernstig astma. [Additional treatments in severe asthma.] 2020. https://richtlijnendatabase.nl/richtlijn/diagnostiek_en_behandeling_van_ernstig_astma/aanvullende_behandelingen_bij_ernstig_astma.html Date last accessed: 8 January 2022.
21 The National Exchange Point. How does it work? 2021. www.volgjezorg.nl/en/lsp. Date last accessed: 10 October 2021.
22 Thomas D, Harvey ES, McDonald VM, *et al.* Mepolizumab and oral corticosteroid stewardship: data from the Australian Mepolizumab Registry. *J Allergy Clin Immunol Pract* 2021; 9: 2715–2724.
23 Silver J, Bogart M, Packnett E, *et al.* Real-world reductions in oral corticosteroid use in the USA following mepolizumab therapy for severe asthma. *J Asthma Allergy* 2020; 13: 689–699.
24 Walsh GM. Eosinophil apoptosis and clearance in asthma. *J Cell Death* 2013; 6: 17–25.
25 Ueki S, Miyabe Y, Yamamoto Y, *et al.* Charcot–Leyden crystals in eosinophilic inflammation: active cytolysis leads to crystal formation. *Curr Allergy Asthma Rep* 2019; 19: 35.
26 Bhalla A, Mukherjee M, Nair P. Airway eosinophilopoietic and autoimmune mechanisms of eosinophilia in severe asthma. *Immunol Allergy Clin North Am* 2018; 38: 639–654.
27 Teague WG, Phillips BR, Fahy JV, *et al.* Baseline features of the Severe Asthma Research Program (SARP III) cohort: differences with age. *J Allergy Clin Immunol Pract* 2018; 6: 545–554.
28 Shaw DE, Sousa AR, Fowler SJ, *et al.* Clinical and inflammatory characteristics of the European U-BIOPRED adult severe asthma cohort. *Eur Respir J* 2015; 46: 1308–1321.
29 Kroes JA, Zielhuis SW, van der Meer AN, *et al.* Optimizing omalizumab dosing in severe asthma – the exploration of therapeutic drug monitoring. *J Allergy Clin Immunol Pract* 2021; 9: 1408–1410.
30 Fahy JV. Type 2 inflammation in asthma – present in most, absent in many. *Nat Rev Immunol* 2015; 15: 57–65.
31 Nanzer AM, Chowdhury A, Raheem A, *et al.* Prevalence and recovery of adrenal insufficiency in steroid-dependent asthma patients receiving biologic therapy. *Eur Respir J* 2020; 56: 1902273.