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## Respiratory Medicine Case Reports

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## Case report

# Effect of benralizumab in a patient with uncontrolled severe eosinophilic asthma and comorbid chronic rhinosinusitis with nasal polyps refractory to mepolizumab treatment

Adel H. Mansur, PhD FRCP

Birmingham Regional Severe Asthma Service, University Hospitals Birmingham NHS Foundation Trust, Heartlands Hospital, Bordesley Green East, Bordesley Green, Birmingham, West Midlands, B9 5SS, United Kingdom

## ARTICLE INFO

## Keywords:

Benralizumab  
Severe eosinophilic asthma  
Biologics  
Eosinophilia  
Chronic rhinosinusitis with nasal polyps

## ABSTRACT

Severe eosinophilic asthma is associated with a high corticosteroid burden, particularly in patients with comorbid chronic sinusitis/nasal polyps. This case study reports a 33-year-old woman who presented to the severe asthma center with uncontrolled severe eosinophilic asthma and chronic rhinosinusitis with nasal polyps (CRSwNP). Despite maximized asthma treatment, including maintenance oral corticosteroids (OCS) for 7 years, the patient experienced one to two hospitalizations per year, had daily symptoms that substantially impacted her quality of life, and elevated type 2 inflammatory markers (blood eosinophils,  $0.72 \times 10^9/L$ ; fractional exhaled nitric oxide, 134 to 300 parts per billion). Her asthma worsened during her first pregnancy, in which she required five hospital admissions despite treatment with maintenance OCS. Mepolizumab treatment was commenced after pregnancy but showed limited efficacy (blood eosinophil levels up to  $0.94 \times 10^9/L$ ); treatment was discontinued because of a second pregnancy. The patient's asthma worsened and resulted in four hospitalizations and an increase in monthly OCS dose. Mepolizumab was recommenced after pregnancy, but her asthma remained uncontrolled, symptoms persisted, and one hospitalization and nine OCS courses were required. The patient was switched to benralizumab treatment when it became available. Although her CRSwNP symptoms remained, benralizumab treatment resulted in a marked improvement in asthma control, zero hospitalizations, and suppressed blood eosinophil levels. Notably, the patient was successfully weaned off maintenance OCS after >11 years of treatment. In summary, these findings support the use of benralizumab as a corticosteroid-sparing treatment option in difficult-to-treat severe eosinophilic asthma refractory to mepolizumab treatment.

## 1. Introduction

Severe asthma is defined as asthma that is uncontrolled despite adherence with optimized high-dose inhaled corticosteroid (ICS) and long-acting  $\beta_2$ -agonist (LABA) treatment and management of contributory factors, or that worsens when high-dose treatment is decreased [1]. Severe asthma is associated with frequent exacerbations that lead to the excessive use of systemic corticosteroids (SCS) that, with their associated side effects, can be burdensome to the lives of patients [2,3]. Adult patients with severe asthma and comorbidities, such as chronic sinusitis/nasal polyps, have been reported to experience frequent asthma exacerbations requiring treatment with SCS [2]. Excessive exposure to long-term SCS is associated with complications such as weight gain, depression, anxiety,

E-mail address: [adel.mansur@uhb.nhs.uk](mailto:adel.mansur@uhb.nhs.uk).

<https://doi.org/10.1016/j.rmcr.2021.101559>

Received 6 July 2021; Received in revised form 18 August 2021; Accepted 23 November 2021

Available online 27 November 2021

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## Abbreviations

ACQ-7	Asthma Control Questionnaire-7
CRSwNP	chronic rhinosinusitis with nasal polyps
FeNO	fractional exhaled nitric oxide
FEV <sub>1</sub>	forced expiratory volume in 1 second
ICS	inhaled corticosteroid(s)
Ig	immunoglobulin
IL	interleukin
LABA	long-acting $\beta_2$ -agonist
NA	not available
OCS	oral corticosteroid(s)
ppb	parts per billion
Q4W	every 4 weeks
Q8W	every 8 weeks
SAC	severe asthma center
SCS	systemic corticosteroid(s)
SMART	Symbicort® Maintenance and Reliever Therapy

sleep apnea, osteoporosis, pneumonia, cardio-cerebrovascular diseases, and renal impairment, among others [3]. Hence, it is vital that such patients are considered for alternative corticosteroid-sparing treatment options [3].

Biologic treatments currently licensed for use in severe asthma include omalizumab (XOLAIR®, Genentech, Inc.; Novartis Pharmaceuticals GmbH; anti-IgE), dupilumab (DUPIXENT®, Sanofi Genzyme; Regeneron Pharmaceuticals, Inc.; anti-IL-4R $\alpha$ ), mepolizumab (NUCALA®, GlaxoSmithKline LLC; anti-IL-5), reslizumab (CINQAIR®/CINQAERO®, Teva Respiratory, LLC; anti-IL-5), and benralizumab (FASENRA®, AstraZeneca AB; anti-IL-5R $\alpha$ ) [4–13]. Benralizumab is approved for use as an add-on maintenance treatment option in patients aged  $\geq 12$  years (USA) and  $\geq 18$  years (Europe) with severe eosinophilic asthma that remains uncontrolled despite treatment with a high-dose ICS and LABA [4,5]. Severe eosinophilic asthma is a phenotype of severe asthma characterized by type 2 inflammation, including high levels of blood and/or sputum eosinophils [1]. The efficacy and safety of benralizumab in severe eosinophilic asthma has been reported in the SIROCCO, CALIMA, and ZONDA Phase 3, randomized controlled trials [14–16]. Across these trials, benralizumab treatment (30 mg every 4 weeks [Q4W]/every 8 weeks [Q8W]) versus placebo demonstrated a depletion in blood eosinophil levels, a significant reduction in exacerbation rate, improved lung function, greater symptom control (Q8W dosing schedule only), and an oral corticosteroid (OCS)-sparing effect [14–16]. In addition to its approved indication, the aim of this real-world case study is to demonstrate the efficacy of benralizumab in uncontrolled severe eosinophilic asthma that did not respond to mepolizumab treatment.

## 2. Case report

A 33-year-old woman was referred to the severe asthma center (SAC) in Birmingham, United Kingdom, in June 2015, following hospitalization for an exacerbation of her late-onset severe non-allergic eosinophilic asthma, which was diagnosed at the age of 20 years. She was a non-smoker who experienced poor asthma symptom control and bothersome nasal symptoms with a history of nasal polyps. Her symptoms developed at the age of 18 years, which had a substantial impact on her previously healthy and physically active lifestyle. The patient had elevated type 2 inflammatory asthma manifesting in raised blood eosinophil levels ( $0.72 \times 10^9/L$ ) and fractional exhaled nitric oxide (FeNO) levels ranging from 134 to 300 parts per billion (ppb). She had significant diurnal variation in her peak expiratory flow rate from 200 to 500 L/min and historical variability in forced expiratory volume in 1 second (FEV<sub>1</sub>) that could normalize (1.83–4.4 L [50–126% predicted]). Her Asthma Control Questionnaire-7 (ACQ-7) score was high at 4.6 (range 0–6; poor control  $\geq 1.5$  [1]). She experienced recurrent lower respiratory tract infections, had prior positive sputum cultures for *Haemophilus influenzae* and *Staphylococcus aureus* infection, and had a computerized tomography scan diagnosis of mild-to-moderate lower zone bronchiectasis.

On presentation to the SAC, the patient's medication regimen consisted of budesonide/formoterol (400/12  $\mu\text{g}$  twice daily), montelukast (10 mg once daily), fluticasone furoate nasal spray (27.5  $\mu\text{g}$  in each nostril once daily), and prophylactic doxycycline (100 mg once daily). The patient was on maintenance OCS treatment (prednisolone, 10 mg once daily), which she had been receiving for 7 years. The OCS dose was increased to 30 mg once daily for 5–7 days during periods of asthma exacerbation; despite this, she had one to two hospitalizations per year. Following multidisciplinary review at the SAC, the patient was referred to a psychologist to address her anxiety and to a physiotherapist for chest clearance exercises and optimization of nasal symptoms. At this time, her treatment was adjusted to include the budesonide/formoterol SMART (Symbicort® Maintenance and Reliever Therapy) regimen, which had previous efficacy for the patient.

Shortly after initial review, the patient became pregnant in June 2015; doxycycline was discontinued, and her care was managed by

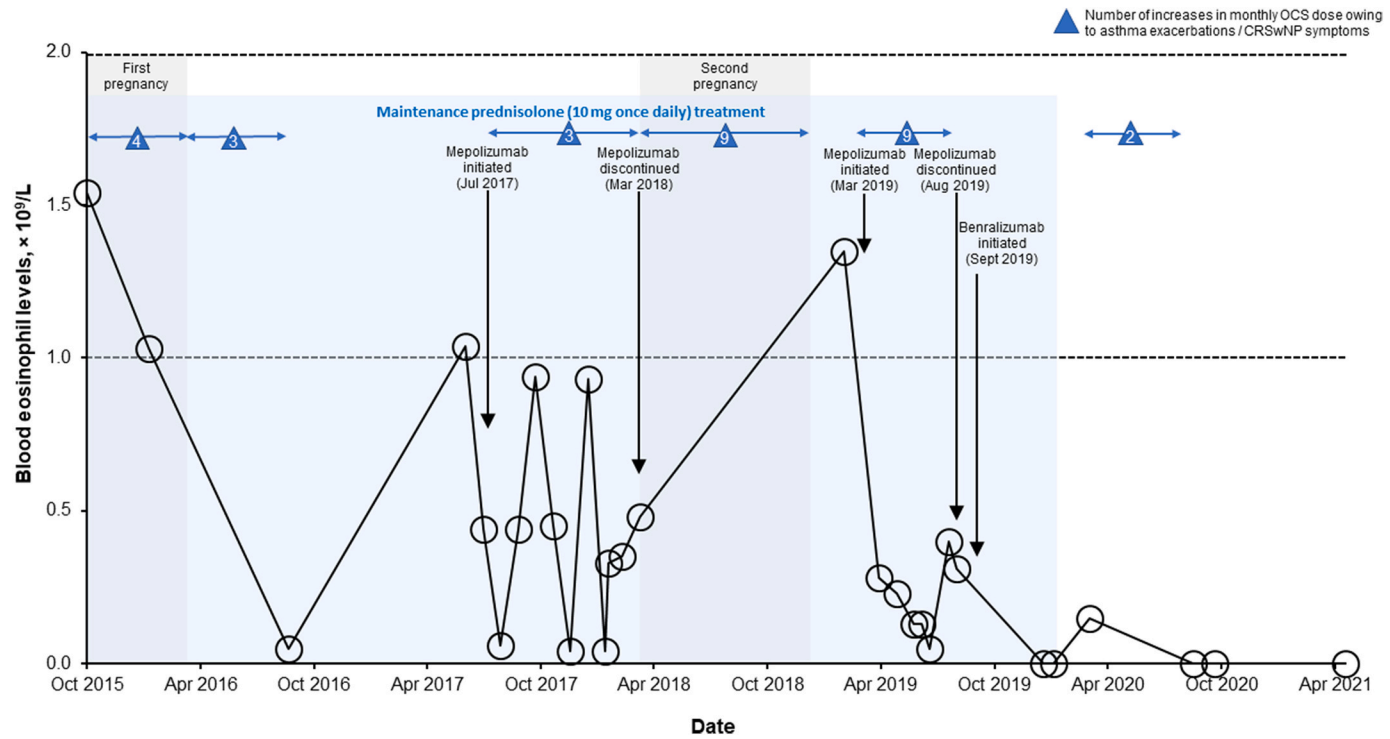


Fig. 1. Blood eosinophil levels over time. CRSwNP, chronic rhinosinusitis with nasal polyps; OCS, oral corticosteroid(s).

a joint antenatal/asthma clinic. While pregnant, she started to experience further worsening of her symptoms (wheeziness, chest tightness, and blocked nose) that required five hospital admissions for stabilization (ACQ-7 score, 4.6). During this time, the patient's blood eosinophil levels remained high at  $1.03 - 1.54 \times 10^9/L$ , and her FeNO levels were 96–208 ppb, with variability in FEV<sub>1</sub> recorded from 2.0 – 3.3 L (57–91% predicted). The variability in the patient's blood eosinophil levels over time is shown in Fig. 1.

In September 2016, the patient was reviewed post pregnancy, having experienced two additional hospitalizations and three increases in OCS treatment dose (blood eosinophil levels,  $0.05 \times 10^9/L$  while on OCS treatment; FEV<sub>1</sub>, 1.6 L [45% predicted]; FeNO levels, 203 ppb; ACQ-7 score, 3.1). Mepolizumab treatment was commenced (100 mg Q4W) in July 2017.

While receiving mepolizumab treatment, improvement in the patient's asthma control remained poor (ACQ-7 score, 4.8). She was unable to reduce her OCS treatment and required three increases in OCS dose. Blood eosinophilia persisted with levels up to  $0.94 \times 10^9/L$  in October 2017, FeNO levels remained high (65–293 ppb), and FEV<sub>1</sub> reduced (1.2–2.9 L [35–83% predicted]). In view of the patient's continued poor asthma control despite mepolizumab treatment, sputum cultures for bacteriology were conducted, and positive results were treated accordingly. Adherence to ICS was confirmed by observation of a 100% prescription-collection history. The patient's persistently raised blood eosinophil level also led to investigations for the presence of comorbidities, including eosinophilic granulomatosis with polyangiitis, allergic bronchopulmonary eosinophilia, eosinophilic pneumonia, and parasitic infection, which were all negative. Due to a second pregnancy in March 2018, mepolizumab was discontinued after 8 months of treatment.

During her second pregnancy, the patient experienced worsening of asthma symptoms, which led to a further four hospital admissions and increases in OCS dose to 30 mg once daily until delivery of her baby (blood eosinophil levels,  $0.48 \times 10^9/L$ ; FeNO levels, 104–116 ppb; FEV<sub>1</sub>, 1.4–2.2 L [40–63% predicted]). Due to the first mepolizumab trial being incomplete, and the lack of access to benralizumab in the National Health Service at the time, the patient recommenced mepolizumab for a second trial in March 2019 for a period of 5 months. However, despite a relative reduction in blood eosinophils to a mean of  $0.22 \times 10^9/L$  (ranging from  $0.05 \times 10^9/L$  while receiving an increased dose of prednisolone [30 mg] once daily to  $0.40 \times 10^9/L$  on the 10 mg/day maintenance prednisolone dose) the patient continued to experience a high disease burden (shortness of breath and wheeze) requiring nine OCS courses, three antibiotic courses, and one hospital admission (ACQ-7 score, 3.7), in addition to the inability to reduce the maintenance dose of oral prednisolone. Consequently, mepolizumab was discontinued and the treatment was switched to benralizumab.

Benralizumab (30 mg Q4W for the first three doses, Q8W thereafter) was started in September 2019. Within 4 months, the patient was gradually weaned off maintenance OCS treatment after an observation of recovery in the adrenal gland function (unsuppressed serum cortisol levels) and blood eosinophil reduction to  $0.00 \times 10^9/L$ . Adherence to OCS treatment over time and recovery of serum cortisol levels following a reduction in OCS treatment while receiving benralizumab are demonstrated in Table 1. After 12 months of benralizumab treatment, the patient reported feeling much better with an improvement in ACQ-7 score from 4.4 to 2.5. During this period, she had one OCS burst for chronic rhinosinusitis with nasal polyps (CRSwNP) and one OCS burst for asthma, but no hospital admissions. Although the patient had substantial improvements in her asthma, nasal blockage persisted, and her FeNO level remained elevated (October 2020, 221 ppb) despite adherence to ICS treatment as measured by the prescription-collection history. The patient has since been referred to the ear, nose, and throat clinic for further management. At the latest assessment conducted in May 2021 (following 20 months of benralizumab treatment), the patient remained well and had not required any additional courses of OCS treatment for her asthma (blood eosinophil level, 0.0 cells/ $\mu L$ ; FeNO, 181 ppb; FEV<sub>1</sub>, 3.4 L [92% predicted]; forced vital capacity, 4.4 L [100% predicted]; ACQ-7 score, 1.8). Treatment outcomes over time are summarized in Table 2.

### 3. Discussion

This case report demonstrated the efficacy of benralizumab treatment in a patient with severe eosinophilic asthma and CRSwNP refractory to mepolizumab treatment. Benralizumab treatment resulted in suppression of her blood eosinophil levels, improved asthma control and symptoms, and discontinuation of maintenance OCS use when previous mepolizumab treatment had been unsuccessful.

Add-on biologic treatment, such as benralizumab or mepolizumab, is recommended in severe asthma when symptoms persist despite high-dose ICS and LABA treatment [1]. Benralizumab (anti-IL-5R $\alpha$ ) and mepolizumab (anti-IL-5) are indicated where there is evidence of an eosinophilic phenotype [1,4,5,8,9], having both demonstrated efficacy in reducing asthma exacerbations and OCS use in patients with severe eosinophilic asthma [14–16,18–20]. Moreover, increased eosinophil levels and comorbid nasal polyps have been identified as predictors of response in patients with severe asthma treated with benralizumab or mepolizumab [1,19,21,22].

Benralizumab has a dual mechanism of action, as it binds to the alpha subunit on the IL-5 receptor of eosinophils, which both inhibits IL-5 cytokines from binding and recruits natural killer cells that perform antibody-dependent cell-mediated cytotoxicity of

**Table 1**

Prednisolone and cortisol assay findings, as measured by liquid chromatography-tandem mass spectrometry, demonstrating suppressed serum cortisol levels (<100 nmol/L) and detectable serum prednisolone levels in keeping with adherence to maintenance prednisolone treatment (10 mg once daily) from 2016 to 2017. Recovery in adrenal function was observed when prednisolone treatment was discontinued in January 2020, as shown by unsuppressed cortisol levels (173 nmol/L) and undetectable serum prednisolone levels (<20 nmol/L) [17].

Date	Prednisolone dose, mg/day	Serum prednisolone level, nmol/L	Serum cortisol level, nmol/L
Apr 2016	10	1490	62
Sep 2016	10	776	23
Nov 2016	10	1370	56
Feb 2017	10	1290	62
Jan 2020	Patient discontinued maintenance prednisolone	<20	173

**Table 2**

Treatment outcomes over time from June 2015 to May 2021.

	Presentation at the SAC (Jun 2015)	First pregnancy (Jun 2015 to Mar 2016)	Mepolizumab treatment (Jul 2017 to Mar 2018)	Second pregnancy (Mar 2018 to Dec 2018)	Mepolizumab treatment (Mar 2019 to Aug 2019)	Benralizumab treatment (Sep 2019 to May 2021)
Mean (range) blood eosinophil levels, $\times 10^9/L$	0.72 <sup>a</sup> (NA)	1.3 (1.03–1.54)	0.40 (0.04–0.94)	0.48 (NA)	0.22 (0.05–0.40)	0.03 (0.0–0.15)
Mean (range) FeNO levels, ppb	208 (NA)	146.0 (96.0–208.0)	176.9 (65.0–293.0)	110.0 (104.0–116.0)	142.2 (72.0–199.0)	230.5 (181.0–300.0)
Maintenance OCS dose, mg/day	10	10	10	10	10	–
Number of additional OCS bursts	4	4	3	9	9	2
Number of hospitalizations	1–2 per year	5	0	4	1	0
ACQ-7 score	4.6	4.6	4.8	2.8 <sup>b</sup>	3.7	1.8
Treatment response <sup>c</sup>	–	Worsening of asthma	No evident benefit; discontinued mepolizumab because of pregnancy	Worsening of asthma	Negative treatment trial	Marked improvement in asthma; residual CRSwNP symptoms

ACQ-7, Asthma Control Questionnaire-7; CRSwNP, chronic rhinosinusitis with nasal polyps; FeNO, fractional exhaled nitric oxide; NA, not available; OCS, oral corticosteroid(s); ppb, parts per billion; SAC, severe asthma center.

<sup>a</sup> Reported January 2008.<sup>b</sup> ACQ-7 was measured while the patient was on an increased dose of prednisolone (30 mg) treatment because of an asthma exacerbation.<sup>c</sup> Based on physician's interpretation of findings on clinical assessment.

eosinophils [1,4,5]. Of note, the complete depletion of blood eosinophil levels reported with benralizumab in this study is consistent with findings from the Phase 3 SIROCCO and CALIMA trials [14,15]. Mepolizumab has demonstrated eosinophil depletion, albeit not complete depletion, in the Phase 3 MENSA trial; however, eosinophilia persisted following mepolizumab treatment in this study [19]. Eosinophil levels were also reduced to a lower level during the second mepolizumab trial than with the first mepolizumab trial; these findings may be the result of a higher number of OCS bursts that were prescribed during the second treatment trial with mepolizumab. Furthermore, the improved efficacy outcomes reported herein with benralizumab versus mepolizumab treatment may be related to the severity of eosinophilic disease requiring a greater degree of eosinophil suppression to achieve a clinically meaningful outcome. However, further evidence is required to determine whether the level of eosinophil suppression with benralizumab correlates with improved efficacy outcomes compared with mepolizumab [23]. Even though the patient showed persistent eosinophilia and a poor treatment response with mepolizumab in this case study, fluctuations in asthma control were observed from presentation at the SAC in January 2015 to August 2019 before initiation of benralizumab treatment. While it was not possible to ascertain deterioration in the patient's asthma when receiving mepolizumab treatment, there was no improvement in asthma control during this time. Of note, no comorbidities were identified that may have impacted the poor treatment response observed with mepolizumab. Although poor adherence to ICS treatment has been found to influence the effectiveness of mepolizumab treatment [24], the patient appeared to be adherent to ICS treatment in this case. Considering the poor treatment response with mepolizumab, biologic treatment would have been ideally switched to benralizumab after 6 months of treatment; however, at the time, benralizumab was not yet available for prescription in the UK. Switching biologic treatment to benralizumab following a suboptimal response to mepolizumab in patients with severe eosinophilic asthma has shown improvements in exacerbation rate, asthma control, OCS use, and/or quality of life in some patients [25,26]. Notably, clinicians should not be discouraged from switching biologics following a poor treatment response with initial biologic therapy, as the mechanism of action can differ between biologics, and patients may have an improved treatment response with a different type 2 targeted therapy [1,25,26].

Mepolizumab has also demonstrated an OCS-sparing effect in severe eosinophilic asthma in the Phase 3 SIRIUS trial, though a reduction in OCS use was not observed in this case study [20]. In contrast, benralizumab enabled the patient to wean off maintenance OCS use 4 months after initiation of benralizumab treatment. These findings are consistent with the Phase 3 ZONDA trial in severe eosinophilic asthma [16]. This OCS-sparing effect is key in reducing the side effects burden associated with corticosteroid use [3,27]. Although OCS have an important role in the management of acute asthma exacerbations, their side effects can result in significant morbidity [27]. Increasing awareness of alternative OCS-sparing treatment options and educating clinicians on the timely referral of patients may help to minimize inappropriate OCS use in patients with asthma [27].

Biologics currently indicated for CRSwNP include dupilumab, omalizumab, and mepolizumab [6,7,9,12,13,28]. Results from the OSTRO (benralizumab) and SYNAPSE (mepolizumab) Phase 3 trials in CRSwNP have demonstrated improvements in nasal polyp score and nasal blockage/obstruction following biologic treatment [29,30]. These findings are supported by studies that found a reduction in nasal polyp size, symptoms, and/or quality of life in the overlap population of patients with severe eosinophilic asthma and CRSwNP treated with benralizumab [31–33]. Furthermore, a randomized, double-blind, placebo-controlled study showed that mepolizumab treatment led to a reduced need for surgery in patients with severe nasal polyps receiving topical corticosteroids [34]. Despite this, benralizumab and mepolizumab did not show an improvement in CRSwNP symptoms in this study. In fact, the patient's FeNO levels were higher after benralizumab treatment versus before, likely because of persistent activity associated with the patient's CRSwNP disease. In addition to IL-5, IL-4 and IL-13 are type 2 inflammatory cytokines associated with CRSwNP [35]. As FeNO levels remained elevated with anti-IL-5/IL-5R $\alpha$  treatment in this study, this suggests that alternative inflammatory mediators, such as IL-4 and IL-13, may be driving the patient's CRSwNP [1,35]. While dupilumab is an anti-IL-4/IL-13 treatment option approved for add-on therapy in adult patients with CRSwNP [12,13], it is not currently available in the UK for the treatment of patients with severe asthma and comorbid CRSwNP.

Additional hypotheses for the patient's elevated FeNO level while receiving benralizumab versus mepolizumab treatment may include reduced corticosteroid use during benralizumab treatment or a lack of adherence to ICS [36]; however, the latter is unlikely in this case, as the patient had a 100% prescription-collection history. Alternatively, it may be that the patient had resistance to ICS treatment that resulted in inadequate suppression of type 2 inflammation and continued high FeNO levels despite adherence to ICS treatment [36,37]. Testing of FeNO-suppression in the presence of ICS adherence may have helped to confirm the presence of an ICS-resistant phenotype in this case study [36,37].

Owing to the limited evidence available for the use of biologics during pregnancy, mepolizumab treatment was discontinued in this case study. Although benralizumab efficacy has previously been reported in a pregnant patient with hypereosinophilic syndrome where complete eosinophil depletion had no safety concerns [38], additional studies are required to support the use of biologic treatment in patients with severe asthma during pregnancy.

#### 4. Conclusion

In summary, this case report demonstrates a marked reduction in corticosteroid use and blood eosinophil levels following benralizumab treatment in a patient with uncontrolled severe eosinophilic asthma refractory to mepolizumab treatment. Although the patient's CRSwNP symptoms persisted, she experienced zero hospital admissions over ~20 months and had a substantial improvement in asthma control following initiation of benralizumab treatment. While benralizumab is indicated as an add-on maintenance treatment option in patients aged  $\geq 12$  years (USA) and  $\geq 18$  years (Europe) with severe eosinophilic asthma [4,5], these findings also support the use of benralizumab as an efficacious, corticosteroid-sparing treatment option in severe eosinophilic asthma refractory to mepolizumab treatment.

## Informed consent statement

Written informed consent was obtained from the patient.

## Data sharing statement

All data requests should be submitted to the corresponding author for consideration. Access to anonymized data may be granted following review.

## Declaration of competing interests

A.H.M. has received research grants, consultant fees, and speaker fees from AstraZeneca, Chiesi, GlaxoSmithKline, Napp Pharmaceuticals, Sanofi, and Teva Pharmaceuticals.

## Author contributions

A.H.M. analyzed and interpreted the patient data, and provided critical review of the manuscript drafts.

## Role of the funding source

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

## Acknowledgments

Medical writing and editing support, including preparation of the draft manuscript in accordance with GPP3 under the direction and guidance of the author, incorporating author feedback and manuscript submission, was provided by Lauren Oswald MSc, of Helios Medical Communications, Alderley Park, Cheshire, UK, and Syed Ali of AstraZeneca, UK. This support was funded by AstraZeneca, UK.

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