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Out of Breath, out of Options: Benralizumab as a Last Hope in ICU-Treated Near-Fatal Eosinophilic Asthma: A Case Series

Lennart Conemans[1,2] | Emel Demir[3] | Martijn Bischoff[4] | Frits Franssen[1,2,5] | Sami Simons[1,2]

[1]Department of Respiratory Medicine, Maastricht University Medical Centre, Maastricht, the Netherlands | [2]NUTRIM Institute of Nutrition and Translational Research in Metabolism, Faculty of Health, Medicine and Life Sciences, Maastricht University, Maastricht, the Netherlands | [3]Department of Respiratory Medicine, Ziekenhuis Maas en Kempen, Maaseik, Belgium | [4]Department of Intensive Care Medicine, Maastricht University Medical Centre+, Maastricht, the Netherlands | [5]Department of Research and Development, Ciro, Horn, the Netherlands

Correspondence: Lennart Conemans (lennart.conemans@mumc.nl)

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ABSTRACT

Asthma exacerbations remain life-threatening events despite advancements in biologic therapies. This case series reports on four patients with near-fatal eosinophilic asthma exacerbations who had been admitted to intensive care and were treated with benralizumab as a last resort after failing maximal standard therapies. All patients exhibited marked blood or airway eosinophilia and required intensive care ventilatory support. Following the administration of benralizumab, significant clinical improvements were observed. This series highlights the potential role of benralizumab in treating life-threatening asthma exacerbations driven by eosinophilic airway inflammation and underlines the need for phenotyping and timely intervention in managing such patients with near-fatal asthma while also stressing the need for continued adherence to asthma guidelines to prevent these extreme situations.

1 | Introduction

Asthma remains a major threat to respiratory health, with up to 300 million people suffering from this condition worldwide [1]. Despite maximal inhaled medication and optimisation of additional factors such as improving adherence, inhalation technique, and comorbidities, some patients still experience symptoms and/or exacerbations. For these patients with severe asthma, several biologic treatments are approved [2]: those targeting Immunoglobulin E (*omalizumab*), interleukin-5 (IL-5; *mepolizumab, reslizumab*), IL-5 receptor (*benralizumab*), IL-4 receptor (*dupilumab*) or thymic stromal lymphopoietin (*tezepelumab*). These therapies have been shown to be effective in improving symptoms and reducing exacerbations [3]. They haven't been approved for the treatment of asthma exacerbations, despite the fact that some of these therapies have a rapid onset of action [4]. Severe asthma exacerbations are not uncommon: in a study of 33,000 hospitalisations for asthma exacerbations, 10% required ICU admission and 2% needed invasive mechanical ventilation [5]. Asthma that does not respond to initial therapy and progresses to respiratory failure is termed near-fatal asthma (NFA). Besides supportive care, treatment of NFA consists of bronchodilators, either nebulised or intravenous, systemic corticosteroids, and magnesium sulphate (MS) [6]. Despite optimal treatment, mortality of NFA is reported to be 10%–25% [5], underlining the search for additional treatment options. In this case series, we report on 4 cases of near-fatal eosinophilic asthma (NFEA) admitted to the ICU of a tertiary referral hospital in the Netherlands where benralizumab was used as a drug of last resort.

2 | Case Series

All patients received maximal supportive and pharmacological therapy for 5–7 days for NFEA between October 2019 and February 2023. After the lack of clinical recovery, benralizumab 30 mg was administered subcutaneously. Eosinophilic granulomatosis with polyangiitis, allergic bronchopulmonary aspergillosis, and hypereosinophilic syndrome were excluded through medical history, organ involvement assessment, laboratory results (IgE, ANCA, urinalysis, and parasitic serology), and chest imaging. Due to the off-label nature of the treatment, it was given after consensus within the multidisciplinary team (MDT) meeting (including intensivist, pulmonologist, ICU nurse, microbiologist) and after discussion with the patients' relatives. Figures 1 and 2 show ventilator peak pressures and respiratory resistances over time for all cases.

2.1 | Case 1

A 48-year-old woman with acute respiratory failure (ARF) due to a severe asthma exacerbation was transferred to the ICU for veno-venous extracorporeal membrane oxygenation (VV-ECMO). She had been suffering from variable dyspnea and cough for the last 6 months, for which her GP prescribed formoterol and 5 courses of oral prednisolone. A documented asthma diagnosis was lacking, and no ICS had been prescribed. She was an active smoker. Based on the typical history combined with raised blood eosinophils (BE; 1800/μL, 12%), a presumptive asthma diagnosis was made.

On admission, chest CT revealed peripheral airway mucus plugs in multiple segments. She was treated with intravenous prednisolone (1 mg/kg), repeated doses of intravenous salbutamol

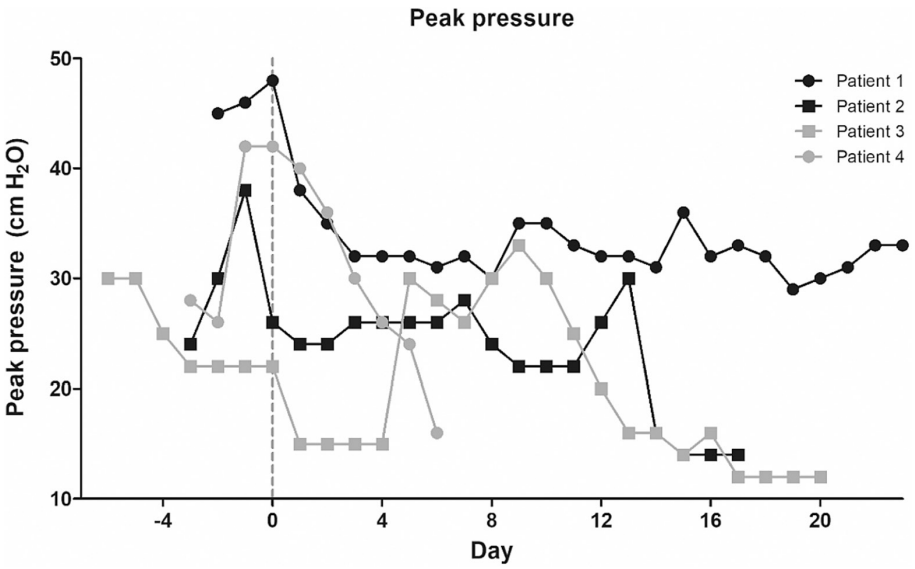

FIGURE 1 | Ventilator peak pressures are shown for the individual patients. On day 0 benralizumab was administered.

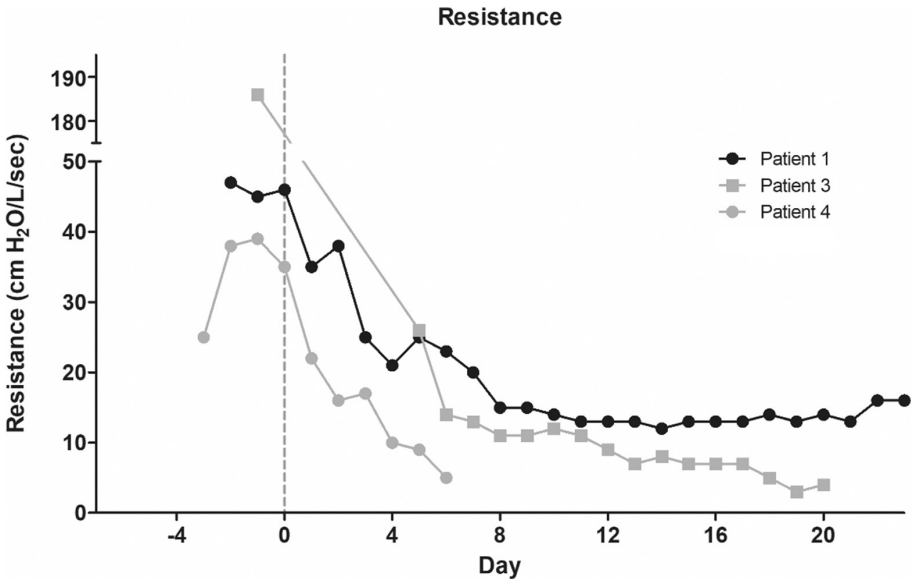

FIGURE 2 | Respiratory system resistance is shown for three patients. On day 0 benralizumab was administered. For patient 2, resistance values are missing because the ventilator's specifications did not allow for this measurement.

(500 μg), MS (2 g) and ceftriaxone/ciprofloxacin for 7 days without signs of improvement in clinical or ventilator parameters. Hypercapnia persisted despite high ventilator pressures, after which benralizumab was given on day 7. In the following days, ventilation pressures could be reduced, and the patient was weaned off ventilation. At follow-up, a diagnosis of asthma was confirmed. She was treated with ICS/LABA and benralizumab, and her asthma has remained well controlled ever since.

2.2 | Case 2

A 65-year-old man, former smoker with a presumed diagnosis of COPD, presented at the emergency department (ED) with ARF and severe bronchospasm. Upon admission, he was promptly intubated and mechanically ventilated, requiring extremely high pressures. Chest CT showed extensive mucus plugging in the lower lobes. On day 5, he deteriorated and became VV-ECMO dependent and required intermittent mandatory ventilation (IMV) with very small tidal volumes. He was treated with intravenous prednisolone (1 mg/kg), salbutamol, and MS, without any improvement in gas exchange or tidal volumes. BE were 1950/μL (14%). Because of a persistent left lower lobe (LLL) atelectasis, a bronchoscopy was performed, which revealed central, viscous mucus plugs. Pathological examination of bronchial washing revealed marked eosinophilia and Charcot-Leyden crystals (CLC). On day 5, he received benralizumab, after which gradual clinical improvement, resolution of atelectasis and removal of VV-ECMO, and extubation occurred after 18 days. During ambulatory follow-up, the diagnosis of COPD was refuted and an asthma diagnosis was confirmed. The patient remained OCS dependent despite maximal therapy, including benralizumab.

2.3 | Case 3

A 62-year-old man with a diagnosis of late onset asthma was admitted to the ED with ARF and wheezing. He was taking ICS/LABA regularly and was a former smoker. The patient was intubated promptly after arrival and admitted to the ICU. Ceftriaxone/ciprofloxacin, prednisolone (1 mg/kg) and salbutamol were started. Two days after intubation, he required support with VV-ECMO. Ventilation was challenging with low tidal volumes and high ventilator pressures. An LLL atelectasis was present. Bronchoscopy was performed to clear the central mucus plugs of the LLL. Bronchial washings showed marked eosinophilia and CLC. BE were 0%; no measurement before prednisolone was done. Because of airway eosinophilia and persistent bronchoconstriction, benralizumab was given on day 7. Subsequent days showed a favourable course with a reduction in ventilator pressures and clearance of the atelectasis by day 7. ICU stay was complicated by endobronchial bleeding and a prolonged weaning trajectory. During follow-up, asthma was well controlled with continued use of benralizumab.

2.4 | Case 4

A 61-year-old man was admitted to the ED with ARF and findings of a silent chest. He was intubated and prednisolone (1 mg/kg), salbutamol, and MS were given. A year before admission, he had been prescribed salbutamol by his GP; no spirometry was done, and no asthma diagnosis was documented. A week before admission, he had received nebulised salbutamol/ipratropium administered by paramedics. He was transferred for evaluation of potential ECMO therapy, which the MDT deemed unnecessary. BE on admission were 1750/μL. A chest CT was not done. Benralizumab was given on day 5 because of the complete lack of improvement. In the following days, he developed ventilator-associated pneumonia. Despite this, a reduction in ventilator pressures was observed. The patient was transferred to the local hospital and was extubated 4 days later. During follow-up, he had well-controlled (confirmed) asthma without the need for a biologic.

3 | Discussion

In this case series, we report on our clinical experience of using benralizumab as rescue therapy for patients with near-fatal eosinophilic asthma exacerbations who did not improve despite maximal guideline-based pharmacologic and supportive therapies. We observed a pronounced improvement in the condition of four patients after the initiation of benralizumab.

The (off-label) treatment of exacerbations with benralizumab has been shown in previous studies. In one case report, a patient with asthma was switched from omalizumab to benralizumab during an exacerbation without the use of systemic corticosteroids. Improvements in symptoms and Forced Expiratory Volume in 1 s (FEV_1) were noted within 48 h [7]. Another case report presented a patient with an eosinophilic exacerbation and a contra-indication for steroids who received benralizumab after 17 days of hospitalisation without improvement: within 24 h, the FEV_1 improved and depletion of sputum eosinophils occurred after 48 hours [8]. Furthermore, benralizumab given as treatment for an exacerbation lowered the incidence of recurrent exacerbations of asthma in the next 12 weeks in a randomised trial [9]. A recent study confirmed that benralizumab can effectively treat exacerbations [10].

This case series provides additional evidence for the efficacy of benralizumab in treating severe exacerbations, extending prior findings to patients with life-threatening conditions. Benralizumab was chosen for its rapid anti-eosinophilic effects [4], with its afucosylated Fc domain inducing active eosinophil apoptosis through NK cell binding. Studies show a 96% reduction in airway eosinophils with benralizumab use [11]. Autopsy findings of mucus plugging, eosinophilia, and CLC in asthma deaths [12] further support the use of targeted anti-eosinophilic therapy like benralizumab in these critical cases. Mucus plugging is well documented in asthma and linked to impaired lung function [13]. Benralizumab has shown potential in reducing mucus plugs, particularly improving symptoms and ventilation in patients with significant mucus plugging [14, 15]. In two cases, mucus clearance was documented, supporting the hypothesis that benralizumab may enhance respiratory function by promoting mucus plug resolution. The therapeutic effect of benralizumab in our cases suggests that non-eosinophilic inflammation is unlikely to play a significant role. Prednisolone's broad anti-inflammatory action and the lack of corticosteroid-sparing effects from any non-type 2 targeted therapies support

this conclusion. While benralizumab also reduces basophil levels, the clinical relevance of this remains uncertain [16], with eosinophil depletion likely being the primary driver of the observed effects.

This study has several limitations. First, it has an observational design, and since we did not systematically collect airway eosinophils before and after treatment, a causal relationship between the initiation of benralizumab and the observed treatment effect cannot be made with certainty. A delayed effect of prednisolone seems unlikely given the persistent eosinophilia, as prednisolone's impact on eosinophilia is reported to be rapid [4]. Second, a higher dose of prednisolone might have been effective, though this is unsupported by current literature. Third, this was a convenience sample of a highly selected patient population that showed evidence of ongoing eosinophilic airway inflammation despite maximal treatment and who were selected after deliberation within an MDT meeting. Our results should thus be appraised within these settings, certainly given the off-label use of benralizumab as treatment of an exacerbation. Future studies should systematically evaluate the safety, timing, and effect of interleukin-5 receptor blockage in NFEA. Some lessons can be drawn as well from this case series. First, late-onset asthma remains a challenging diagnosis, especially in former or current smokers who may be incorrectly labelled as COPD. Second, incorrect diagnosis or treatment, leading to the omission of ICS prescription, can have severe consequences. These factors have long been recognised as contributors to preventable asthma deaths [17] and underscore that ICS remain the cornerstone in the management of asthma. Third, the combination of corticosteroid-resistant "asthmatic state" with markedly raised blood eosinophil count and/or persistent airway eosinophilia is an extremely severe situation sometimes necessitating ICU admission and ECMO. Cytological examination of sputum or bronchial washing for eosinophils aids in identifying the eosinophilic endotype of the exacerbation. This study showed that in the case of ongoing eosinophilic inflammation, therapy with benralizumab might be of benefit.

In conclusion, this case series highlights the potential of benralizumab as a rescue treatment in NFEA and may inform future studies that should implement a concise protocol for workup, add-on treatment selection, and follow-up of these patients.

Author Contributions

L.C. conceived the study idea. L.C. and E.D. wrote the first draft of the manuscript. L.C., E.D., and M.B. were responsible for the acquisition of the data. M.B. provided the images. All authors (L.C., E.D., M.B., F.F., and S.S.) contributed to the interpretation of findings. Each author revised the manuscript critically for intellectual content and approved the final version for publication.

Ethics Statement

The authors declare that appropriate written informed consent was obtained for the publication of this manuscript and accompanying images.

Conflicts of Interest

L.C. received honoraria for lectures from AstraZeneca, GlaxoSmithKline, and Sanofi. He is indirectly involved in a research grant provided by AstraZeneca. F.F. received honoraria for lectures and consultancies from AstraZeneca, Chiesi, GlaxoSmithKline, MSD, Pfizer, and Sanofi. In addition, he received scientific writing support from AstraZeneca, Chiesi, and Novartis. Also, he received research grants from AstraZeneca. S.S. received grants from Roche, Dutch Research Council, and Lung foundation Netherlands. Also, he received honoraria for lectures and consultancies from AstraZeneca, Chiesi, and GlaxoSmithKline.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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