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Case Report

Tezepelumab in a case of severe asthma exacerbation and influenza-pneumonia on VV-ECMO

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ABSTRACT

We present a case of 43-year-old male patient with broadly by Omalizumab, Mepolizumab and Benralizumab pretreated allergic asthma, who suffered a near fatal exacerbation, triggered by an influenza A infection. Due to massive bronchoconstriction with consecutive hypercapnic ventilatory failure veno-venous ECMO therapy had to be implemented. Hence, guideline directed asthma therapy a substantial bronchodilatation could not be achieved. After administration of a single dose Tezepelumab, a novel TLSP-inhibitor, and otherwise unchanged therapy we documented a significant reduction in intrinsic PEEP measured via a naso-gastric balloon catheter and a narrowing in the expiratory flow curve of the ventilator within 24 hours. The consecutive ventilatory improvement allowed the successful weaning from veno-venous ECMO therapy and invasive ventilation.

1. Introduction

Biologics targeting eosinophilic or allergic inflammation have resulted in a significant decrease in disease-related exacerbation rates and systemic corticosteroid use in patients with severe asthma, both in clinical trials and real-world studies [1]. Despite these therapeutic options, some patients continue to experience severe exacerbations [2,3]. In this context respiratory viruses, such as influenza, play a role in up to 80 % of asthma exacerbations [4,5]. We report a case of a 43-year-old male patient with previously known severe asthma, who presented with acute respiratory failure following an influenza infection, requiring mechanical ventilation and VV-ECMO therapy. The patient was successfully weaned off mechanical ventilation and extracorporeal support few days following Tezepelumab therapy, a novel TLSP-inhibitor in asthma.

2. Case presentation

A 43-year-old male patient with previously diagnosed severe persistent asthma presented with progressive dyspnoea and clinical signs of infection combined with severe bronchospasm, refractory to initial pharmacologic management, to the emergency department of our hospital. Previous medical history reveals a broadly pre-treated, but still uncontrolled asthma, with a mixed phenotype. There was evidence of allergy with sensitization against house dust mite, animal hair, and pollen (last documented total IgE 293 U/ml), as well as eosinophilia as high as 1,09 G/L. The respiratory condition was aggravated by comorbid obesity (BMI: 35.1 kg/sqm) with obstructive sleep apnoea. There was no evidence of nasal polyps or chronic rhinosinusitis. The patient was on inhaler therapy

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with high-dose ICS/Formoterol (1280 mcg Budesonide/day), antihistaminic therapy, and oral Theophylline. Regarding his biological therapy the patient previously received Omalizumab in 2011, followed by Mepolizumab in 2017, and Benralizumab in 2019. Despite these there was no sufficient asthma control. One month prior to this hospital admission the patient was recommended a rechallenge therapy with Mepolizumab by his treating physician (see Tables 1 and 2).

The patient was admitted to the intensive care unit and had to be intubated due to severe respiratory failure after an unsuccessful trial of non-invasive ventilation. Arterial blood gas analysis on arrival was pH 7.07, paCO2 112 mmHg, and paO2 127 mmHg at 80 % FiO2 on mechanical ventilation. An influenza A infection was diagnosed via PCR from tracheal aspirates. The patient received Oseltamivir (75mg twice daily) and empiric antibiotic therapy (Ceftriaxone, 4g, intravenous, once daily), in the presence of elevated inflammatory markers and bilateral infiltrates on chest-x ray per current recommendations [6]. Due to severe bronchospasm, both high dose inhaled bronchodilators and systemic corticosteroids (prednisolone 0.5 mg/kg/day) were given. 24 hours after intubation there was persistent severe respiratory acidaemia despite exhausting ventilatory strategies. (FiO2: 80 %, PEEP: 20mbar, Ppeak: 50mbar). Ventilator settings were adjusted according to the transpleural pressure gradient, measured via a naso-gastric balloon catheter and intrinsic PEEP measurements as well as the statically measured intrinsic PEEP. PEEP (extrinsic) was set 10 % below the measured intrinsic PEEP, with the aim of preventing collapse of the airways during expiration. The respiratory time ratios were chosen in such a way that no early termination of expiratory flow occur. Due to persistent carbon dioxide retention (paCO2 of 112 mmHg, pH 7.07) VV-ECMO therapy was initiated using a femoro-jugular access at a blood flow of 4.8 l/min. Gas flow was slowly increased to 5 l/min to achieve balanced pH values. Initial ventilator settings after the initiation of VV-ECMO using above approach were PEEP 13mbar, pPeak 36mbar, and I:E ratio 1:3,4. After 24 hours of ECMO-therapy improvements in arterial blood gases were observed (pH 7.38, paCO2 61 mmHg, paO2 94 mmHg). In the following days the antibiotic regimen had to be extended to cover pseudomonas aeruginosa due to a diagnosis of ventilator-associated-pneumonia. After twelve days of VV-ECMO therapy the patient, however, continued to pre-

Table 1
Medical history.

Abbreviations: BMI: body mass index; CPAP: continuous positive airway pressure; mg: milligrams; s/p: status post

- Allergic asthma bronchiale Stage IV
- s/p therapy trial with Omalizumab, Mepolizumab, Benralizumab
- Current „rechallenge“ with Mepolizumab (last administration of 100mg in November 2022)
- s/p severe exacerbation in March 2018, with ICU-admission
- Obstructive sleep apnoea
- without nocturnal CPAP
- Nicotine dependency
- s/p umbilical hernia
- laparoscopic hernia repair
- Adipositas grade 1 (BMI: 35.1)
- Allergies: pollen, cat hair, house dust

Table 2a
Home medication prior to admission.

Abbreviations: µg: micrograms; mg: milligrams

Drug	Dosage	Indication
Budesonide + Formoterol	Inhalation 640µg twice daily	Allergic asthma bronchiale
Mometasone	Nasal 100µg Once daily	Allergic rhinitis
Levocetirizine	Oral 5mg Once daily	Allergic asthma bronchiale
Theophylline	Oral 300mg retard Once daily	Allergic asthma bronchiale
Mepolizumab	100mg every four weeks	Allergic asthma bronchiale
Prednisolone	As needed	Allergic asthma bronchiale
Fenoterol + Ipratropium bromide	As needed	Allergic asthma bronchiale

Table 2b
prior asthma-specific targeted therapy.

Note: reported hospital admission: December 2022

Drug	Dosage	Date
Mepolizumab	100 mg	April 2022 - November 2022
Benralizumab	30 mg	February 2019–June 2019
Mepolizumab	100 mg	June 2017–March 2018
Omalizumab	600 mg	April 2011–February 2012

Table 3
Spirometric values prior and after hospital admission.

Abbreviations: n.a.: not available; FEV1: forced expiratory volume in 1 s; FVC: forced vital capacity; Diff FEV1: changes in FEV1 after bronchodilatation; VC max: maxim vital capacity; % pred: percentage of predicted value,

Date	November 2015	March 2016	July 2017	November 2018	July 2019	January 2020	November 2021	April 2022	March 2023
FEV1 % VC	51	51	46	36	37	38	51	45	61
FEV1 post lyse [% pred]	34	37	29	21	21	21	27	25	33
Diff FEV1 [%]	n.a.	+3	+3	n.a.	n.a.	−1	+4	n.a.	+5
VC max [% pred]	57	62	53	49	48	46	43	45	52
									After discharge

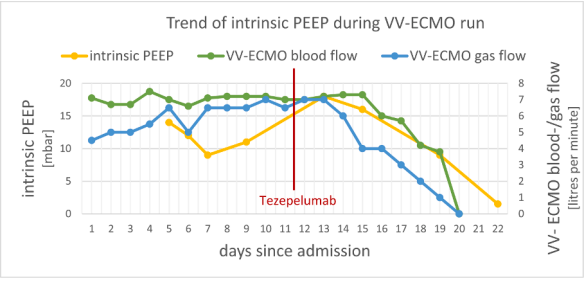

Fig. 1. Trend of intrinsic PEEP during VV-ECMO run.

sent with severe bronchospasm on mechanical ventilation, despite continued high dose inhaled bronchodilator treatment, intravenous magnesium sulfate, and intermittent muscle relaxant therapy.

Based on the patient's previous medical history with rather modest response to high-dose ICS/LABA and anti-IL 5 therapy and the current refractory condition, a team decision was made to administer a therapeutic off-label trial with Tezepelumab (210mg, subcutaneously). This new monoclonal antibody against thymic stromal lymphopoietin, significantly reduced the rate of severe asthma exacerbation in pre-treated and still uncontrolled patients and is therefore approved as a maintenance therapy [7]. The patient received 210 mg subcutaneous Tezepelumab on the thirteenth day after hospital admission. No side effects were observed.

With otherwise unchanged therapy, improvements were seen in the expiratory flow curve of the ventilator within 24 hours, followed by stepwise reduction in VV-ECMO support levels in the following days. The patient was successfully weaned of VV-ECMO therapy on day seven after Tezepelumab. Due to previous high dose sedation medication and muscle relaxation full weaning from mechanical ventilation took another 13 days. The patient was subsequently transferred to the normal ward and underwent pulmonary rehabilitation recently (Table 3 and Fig. 1).

3. Discussion

To the best of our knowledge, this is the first case of a patient treated with Tezepelumab for near fatal asthma due to an influenza-associated exacerbation, requiring mechanical ventilation and extracorporeal CO2 removal via VV-ECMO.

Several structural and inflammatory changes have been described in fatal and near-fatal asthma, such as smooth muscle hypertrophy and hyperplasia, increased extracellular matrix deposition in the airway walls, neutrophils, mast cells and eosinophils. However, the hallmark of near fatal asthma is intense mucus plugging and goblet cell hyperplasia, ultimately, leading to airway casts obstructing small and large airways [8]. Most type 2 cytokines are involved in this process contributing to mucus plugging.

Tezepelumab was approved in December 2021 by the US Food and Drug Administration (FDA) and was available for use in Austria since September 2022. This new human monoclonal IgG2λ antibody unfolds its effects by binding to the thymic stromal lymphopoietin (TSLP) preventing TSLP from interacting with the heterodimeric TSLP receptor. Blocking TSLP reduces biomarkers and cytokines associated with inflammation including eosinophils, IL-5, IL-13, IgE, FeNO [9]. TSLP is released from the epithelial cells as a response to exogenous triggers. Due to its upstream activity in the inflammation cascade it may be suitable for a broad population of patients with severe asthma (type 2 and non-type 2) [10]. A phase 2 study showed a significant reduction in airway submucosal eosinophil count after Tezepelumab treatment compared to placebo - regardless of baseline blood eosinophil count [11]. The consecutive phase 3 study showed sustained efficacy in reduction of asthma exacerbations [12].

Sverrild et al., demonstrated a in vivo reduction in cytokine response of airway epithelia after viral contact [13].

Similar to the case presented here previous case reports have described the application of other biologics, such as Reslizumab or Benralizumab in patients with acute severe asthma exacerbations, with the intention of eosinophil depletion within 24 hours in patients with a predominantly eosinophilic type of asthma [14–16]. In patients already receiving anti-IL5 drugs, as in our case report, exacerbations seem to be predominantly non-eosinophilic in nature [17,18]. Tezepelumab is the first available biological therapy that

appears to be effective in non-eosinophilic/non-type 2 asthma phenotypes, too, which makes it an attractive option in acute severe asthma exacerbations pre-treated with other biologics.

While we believe that the patient had primarily responded to Tezepelumab, given the rapid clinical improvements observed following application, we obviously cannot rule out that clinical was independent of the biological therapy applied.

In summary, we presented a case of 43-year-old male patient with broadly pretreated asthma, who suffered a near fatal exacerbation. Due to massive bronchoconstriction with consecutive ventilatory failure VV-ECMO therapy had to be implemented. Hence, guideline directed asthma therapy a substantial bronchodilatation could not be achieved. We documented a significant ventilatory improvement after administration of a single dose Tezepelumab.

CRediT authorship contribution statement

E. Grasmuk-Siegl: Writing – review & editing, Writing – original draft, Conceptualization. **E. Xhelili:** Writing – original draft, Data curation. **D. Doberer:** Writing – review & editing. **M.H. Urban:** Writing – review & editing. **A. Valipour:** Writing – review & editing, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Abbreviations

FDA	US Food and Drug Administration
FiO2	fraction of inspired oxygen
I:E	ratio between inhalation and exhalation time in the breathing cycle
IgE	Immunoglobulin E
IL-7	Interleukin 7
l/min	litres per minute
mbar	millibar
mg/kg/day	milligrams per kilograms per day
mmHg	millimetre of mercury
PCR	polymerase chain reaction
pCO2	partial pressure of carbon dioxide
PEEP	positive end-expiratory pressure
pO2	partial pressure of oxygen
pPeak	peak-pressure
TSLP	Thymic stromal lymphopoietin VV-ECMO veno-venous extracorporeal membrane oxygenation

References

[1] F. Abbas, S. Georas, X. Cai, S. Khurana, Asthma biologics: real-world effectiveness, impact of switching biologics, and predictors of response, Ann Allergy Asthma Immunol Off Publ Am Coll Allergy Asthma Immunol. Dezember 127 (6) (2021) 655–660.e1.

[2] L. Pérez de Llano, C. Cisneros, J. Domínguez-Ortega, E. Martínez-Moragón, J.M. Olaguibel, V. Plaza, a u, Response to monoclonal antibodies in asthma: definitions, potential reasons for failure and therapeutic options for suboptimal response, J Investig. Allergol. Clin. Immunol. 30 (August 2022;0).

[3] A. Bourdin, J. Charriot, C. Boissin, E. Ahmed, C. Suehs, A. De Sevin, a u, Will the asthma revolution fostered by biologics also benefit adult ICU patients? Allergy 76 (8) (August 2021) 2395–2406.

[4] W.C. Tan, Viruses in asthma exacerbations, Curr Opin Pulm Med. Januar 11 (1) (2005) 21–26.

[5] B. Sposato, L. Croci, E. Canneti, M. Di Tomassi, M.G. Migliorini, A. Ricci, a u, Influenza A H1N1 and severe asthma exacerbation, Eur Rev Med Pharmacol Sci. Mai 14 (5) (2010) 487–490.

[6] G. Höffken, J. Lorenz, W. Kern, T. Welte, T. Bauer, K. Dalhoff, a u, Kurzfassung der S3-Leitlinie zu ambulant erworbenen unteren Atemwegsinfektionen sowie zu ambulant erworbener Pneumonie bei Erwachsenen. DMW - Dtsch Med Wochenschr, Februar 135 (8) (2010) 359–365.

[7] Roy P, Rafa ZI, Haque SN, Tasha T, Arko SB, Agrawal H, u. a. The impact of tezepelumab in uncontrolled severe asthma: a Systematic review of Randomized controlled trials. Cureus. 14(12):e32156.

[8] G. Varricchi, S. Ferri, J. Pepys, R. Poto, G. Spadaro, E. Nappi, a u, Biologics and airway remodeling in severe asthma, Allergy. Dezember 77 (12) (2022) 3538–3552.

[9] M.G. Matera, P. Rogliani, L. Calzetta, M. Cazzola, TSLP inhibitors for asthma: current Status and Future Prospects, Drugs 80 (5) (April 2020) 449–458.

[10] J. Feist, M. Lipari, P. Kale-Pradhan, Tezepelumab in the treatment of uncontrolled severe asthma, Ann Pharmacother. Januar 57 (1) (2023) 62–70.

[11] S. Diver, L. Khalfaoui, C. Emson, S.E. Wenzel, A. Menzies-Gow, M.E. Wechsler, a u, Effect of tezepelumab on airway inflammatory cells, remodelling, and hyperresponsiveness in patients with moderate-to-severe uncontrolled asthma (CASCADE): a double-blind, randomised, placebo-controlled, phase 2 trial, Lancet Respir. Med. 9 (11) (November 2021) 1299–1312.

[12] A. Menzies-Gow, M.E. Wechsler, C.E. Brightling, S. Korn, J. Corren, E. Israel, a u, Long-term safety and efficacy of tezepelumab in people with severe, uncontrolled asthma (DESTINATION): a randomised, placebo-controlled extension study, Lancet Respir. Med. 11 (5) (2023) 425–438 Mai.

[13] A. Sverrild, S. Cerps, J.J. Nieto-Fontarigo, S. Ramu, M. Hvidtfeldt, M. Menzel, a u, Tezepelumab decreases airway epithelial IL-33 and T2-inflammation in response to viral stimulation in patients with asthma, Allergy 17 (2023) Oktober.

[14] A. Renner, K. Marth, L. Schäffl-Doweik, W. Pohl, Reslizumab in an invasively ventilated patient with acute respiratory failure, J Allergy Clin Immunol Pract. Dezember 7 (8) (2019) 2922–2923.

[15] S. Ramakrishnan, J.R. Camp, B. Vijayakumar, F.M. Hardinge, M.L. Downs, R.E.K. Russell, a u, The Use of benralizumab in the treatment of near-fatal asthma: a new approach, Am J Respir Crit Care Med. 1. Juni 201 (11) (2020) 1441–1443.

[16] L. Pérez de Llano, N. Blanco Cid, M. Ortiz Piquer, D. Dacal Rivas, Compassionate Use of a single dose of benralizumab in a near-fatal asthma exacerbation, J Investig Allergol Clin Immunol. 22. Juni 31 (3) (2021) 268–270.

[17] R. Shrimanker, I.D. Pavord, S. Yancey, L.G. Heaney, R.H. Green, P. Bradding, a u, Exacerbations of severe asthma in patients treated with mepolizumab, Eur Respir J. Dezember 52 (6) (2018) 1801127.
[18] S.M. Poznanski, M. Mukherjee, N. Zhao, C. Huang, K. Radford, A.A. Ashkar, a u, Asthma exacerbations on benralizumab are largely non-eosinophilic. Allergy, Januar 76 (1) (2021) 375–379.