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Case Report

Tezepelumab in near-fatal asthma requiring VV-ECMO

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ABSTRACT

Phase III studies have demonstrated that the anti-TSLP biologic tezepelumab significantly reduces asthma exacerbations in severe asthma, regardless of endotype. However, evidence on its use in near-fatal asthma is lacking. Tezepelumab's ability to reduce bronchial hyperresponsiveness and ILC2, eosinophil, and mast cell activation may contribute to attenuating severe exacerbations.

We report the case of a 44-year-old female active smoker (25 pack-years) with a six-month history of asthma, admitted to the ICU with near-fatal asthma triggered by influenza A infection. Orotracheal intubation and invasive ventilation were required. Due to persistent ventilatory failure and acidaemia despite high-pressure ventilation, VV-ECMO was initiated. Treatment included oseltamivir, high-dose intravenous steroids, magnesium, and salbutamol. Attempts to reduce sedation repeatedly induced severe bronchospasm.

After five days on VV-ECMO, given the critical condition and lack of asthma endotype data, azithromycin 250 mg every other day and tezepelumab 210 mg were administered to achieve a potent anti-inflammatory effect. Within 48 hours of tezepelumab administration, progressive weaning from VV-ECMO and ventilation was possible, leading to successful extubation. The patient was transferred to the pulmonology unit for rehabilitation. Forced oscillation techniques revealed reduced reactance and increased resistance at 5 Hz, both improving one month post-discharge.

This is the second reported case of near-fatal asthma requiring VV-ECMO treated with tezepelumab, and the first in a patient without prior asthma diagnosis. Biologic therapy in acute settings may improve outcomes in refractory near-fatal asthma, warranting further clinical investigation.

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1. Introduction

Phase III studies have shown that tezepelumab, an anti-thymic stromal lymphopoietin (TSLP) biologic drug, significantly reduces the risk of asthma exacerbations in patients with severe asthma, regardless of the underlying endotype [1–4]. TSLP expression is increased in patients with asthma compared with healthy controls. Released by epithelial cells in response to tissue damage caused by viruses, bacteria, and cigarette smoke [5], its levels correlate with disease severity and the risk of asthma exacerbations [6–8]. Although the existing literature does not address the use of this treatment in acute asthma, its potential to reduce bronchial hyperresponsiveness and to inhibit the activation of type 2 innate lymphoid cells (ILC2), eosinophils, and mast cells may play a role in the acute phase of severe asthma exacerbations.

We report the case of a 44-year-old female active smoker with no reported allergies and a six-month history of asthma who was admitted to the Intensive Care Unit (ICU) with near-fatal asthma and severe bronchospasm requiring invasive ventilation and Veno-venous Extracorporeal Membrane Oxygenation (VV-ECMO).

2. Case report

A 44-year-old female active smoker (25 pack-years) with no reported allergies or documented diagnosis of asthma was admitted to the ICU with near-fatal asthma and severe bronchospasm requiring invasive ventilation and VV-ECMO.

Over the previous six months, the patient had experienced monthly asthma episodes characterized by wheezing and chest tightness, which resolved with the use of inhaled salbutamol.

One week before ICU admission, she was admitted to the emergency department of a secondary care hospital with acute asthma leading to respiratory failure. She was treated with intravenous (IV) methylprednisolone, nebulized short-acting β_2-agonist, nebulized steroid and supplemental oxygen. She was discharged with oral methylprednisolone (16 mg daily for three days) and umeclidinium bromide/vilanterol therapy. Following an initial favorable response, the patient returned to the emergency department a few days later with a second episode of acute dyspnoea.

On admission, she presented with severe bronchostenosis with hypoxic-hypercapnic respiratory failure and marked respiratory acidosis, refractory to IV pharmacological therapy (1 mg/kg bolus methylprednisolone, magnesium and bronchodilators) and to non-invasive ventilation (NIV). She underwent orotracheal intubation and invasive mechanical ventilation.

Due to persistent ventilatory failure resulting in acidaemia despite a high-pressure invasive ventilation strategy, VV-ECMO was initiated 2 h later (gas flow 4 L/min and blood flow 4.5 L/min). VV-ECMO was implanted by the mobile ECMO team from Careggi University Hospital, as the patient was not transportable. After stabilisation on VV-ECMO, she was transferred to the tertiary ICU at Careggi University Hospital for further management.

A total-body CT scan showed pneumomediastinum and consolidation of the upper left lobe and lingula. Bronchoalveolar lavage (BAL) was performed, and Influenza A PCR tested positive.

The patient was treated with IV methylprednisolone (40 mg twice daily) and oseltamivir. IV salbutamol was administered until lung ventilation resumed, after which point it was replaced by nebulized salbutamol, ipratropium bromide and beclomethasone via the orotracheal tube. Due to haemodynamic instability, a norepinephrine infusion was initiated.

After four days of maximal treatment, the patient could not be weaned from VV-ECMO. Repeated attempts to reduce sedation resulted in rapid onset of bronchospasm and a sudden reduction in tidal volume, requiring increased ventilation and VV-ECMO support (Fig. 1).

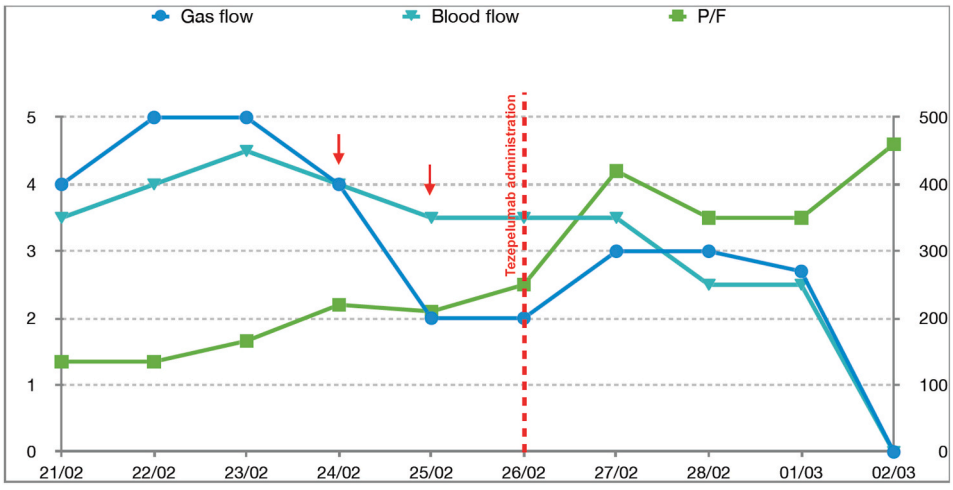

Fig. 1. Trends of gas flow, blood flow, and PaO2/FiO2 (P/F) ratio from February 21 to March 2. The red dashed line indicates the time of tezepelumab administration. Awakening trials failed due to the onset of severe bronchospasm, decreased VT and desaturation.

On the fifth day of VV-ECMO, the Severe Asthma Unit Team of Careggi University Hospital evaluated the patient who had neither previous tests documenting asthma nor the endotype and decided to administer azithromycin treatment (250 mg every other day via nasogastric tube) and tezepelumab (210 mg subcutaneously).

Following administration, the PaO2/FiO2 ratio shows a progressive improvement. The reduction in gas flow and blood flow reflects a favorable clinical evolution, indicating that VV-ECMO support was progressively less necessary (Fig. 1).

Forty-eight hours after the administration of tezepelumab, the patient's VV-ECMO support was gradually reduced until it was discontinued 72 h after the administration.

The patient underwent a spontaneous breathing trial, which was successful, and was extubated two days after tezepelumab administration.

The patient was moved to the pulmonology ward and underwent pulmonary rehabilitation. Forced oscillation techniques (FOT) were performed during hospitalization twelve days after spontaneous breathing. Reduced reactance and increased resistance at 5Hz were found, improving both one month after discharge (Fig. 2).

3. Discussion

To the best of our knowledge, this is the second reported case of a patient treated with tezepelumab for near-fatal asthma due to an influenza-associated exacerbation, requiring mechanical ventilation and VV-ECMO support [9].

Differently from the case reported [9], our patient was a female smoker with late-onset disease and no previous history of asthma, presenting with a type 2-low inflammatory profile. This clinical pattern is often associated with reduced responsiveness to corticosteroids and a predominantly neutrophilic or mixed airway inflammation, which can contribute to a more severe and refractory disease course. The clinical improvement observed after tezepelumab administration suggests that TSLP inhibition may represent an effective therapeutic approach in this type of inflammatory profile, modulating the acute inflammatory response and facilitating rapid clinical recovery.

The rationale of tezepelumab employment in this case is based on its mechanism of action: by TSLP, an epithelial alarmin released in response to inflammatory insults of bronchial epithelium such as pollutants, infections, physical agents. Tezepelumab inhibits downstream activation of multiple inflammatory pathways, including type 2 cytokines but also neutrophils and mast cells. In this context, we hypothesized that early suppression of TSLP-driven inflammation could reduce bronchial hyperresponsiveness and attenuate the exaggerated airway inflammatory response triggered by influenza infection, thereby facilitating recovery from severe bronchospasm and respiratory failure [5–7]. The rapid clinical improvement observed after tezepelumab administration, with the possibility of weaning from VV-ECMO within 48 h, supports the hypothesis that TSLP blockade may modulate airway inflammatory response even in acute, virus-induced, severe asthma exacerbations. Although current evidence regarding the use of biological therapies in acute severe asthma and during VV-ECMO support remains limited, this case provides additional evidence supporting the potential role of TSLP blockade as a rescue strategy in refractory, virus-induced asthma exacerbations, regardless of the underlying inflammatory endotype. Further studies are needed to confirm these observations and to better define the role of biologic drugs particularly tezepelumab in the management of life-threatening asthma.

CRediT authorship contribution statement

Elisa Bentivegna: Conceptualization, Visualization, Writing – original draft, Writing – review & editing. **Greta Insalata:** Conceptualization, Visualization, Writing – original draft, Writing – review & editing. **Luca Paita:** Conceptualization. **Alessia Catalisano:** Conceptualization. **Chiara Allegrini:** Conceptualization, Supervision. **Giovanni Cianchi:** Supervision, Writing – review & editing. **Manuela Bonizzoli:** Supervision. **Federico Lavorini:** Supervision. **Gianna Camiciottoli:** Conceptualization, Supervision, Writing – review & editing.

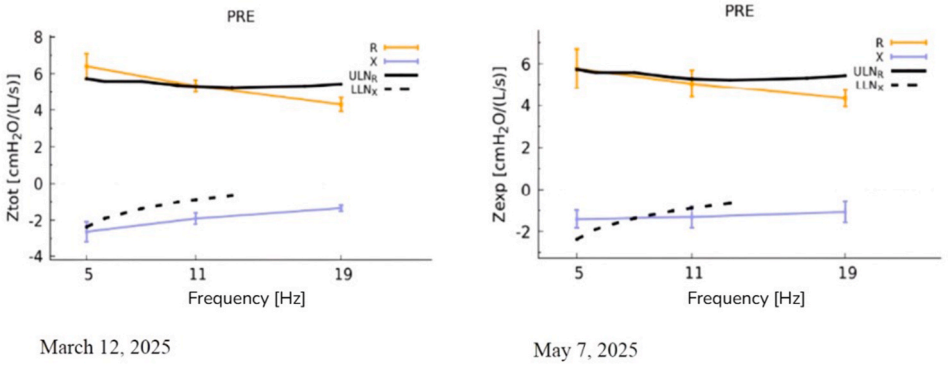

Fig. 2. Resistances and reactance were measured using FOT at discharge and after 2 months. It was observed that reactance decreased, while resistance increased at 5, 11 and 19 Hz.

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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.

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Glossary

BAL	Bronchoalveolar lavage
FOT	Forced oscillation techniques
ILC2	inhibit type 2 innate lymphoid cells
IV	intravenous
NIV	non-invasive ventilation
TSLP	thymic stromal lymphopoietin
VV-ECMO	Veno-venous Extracorporeal Membrane Oxygenation

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