Near fatal asthma: Acute effect of omalizumab in paediatric patient undergoing extracorporeal carbon dioxide removal (ECCO₂R)

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Abstract

Objective: Severe status asthmaticus not responsive to therapy are not a prerogative of severe asthma. We report the case of a severe status asthmaticus refractory to medical therapy, undergoing Invasive Mechanical Ventilation (IMV) and extra-corporeal carbon dioxide removal (ECCO₂R). Since it was life-threatening situation, the equip decided to administer off-label Omalizumab, a drug with an anti-IgE action.

Data synthesis: After the drug administration patients clinically improved, White Blood Cell (WBC) count in Broncho-Alveolar Lavage (BAL) decreased rapidly and the patient can be weaned from ECCO₂R and IMV. Finally, patient was discharged from ICU to hospital ward and then to home.

Conclusion: Off-label use of Omalizumab provided a fast WBC reduction in BAL and fast recovery in a paediatric severe status asthmaticus refractory to all treatment.

Abbreviations


Introduction

Severe asthma is a life-threatening condition that is particularly challenging in patients who do not respond to conventional therapy [1]. In critically ill patients admitted with severe asthma, Invasive Mechanical Ventilation (IMV) is often required to stabilize the respiratory status. Anaesthetic medical drugs in combination with Extracorporeal Carbon Dioxide Removal System (ECCO₂R) are well-described rescue therapies used to treat patients suffering from severe status asthmaticus [1].
In particular, the use of extracorporeal carbon dioxide removal system (ECCO\textsubscript{2}R) has been proposed as a bridge therapy to curb hypercapnia and acidosis [8-10].

The medical treatment of asthmatic access does not involve the use of biological drugs, which are usually used for its prevention. Among them, omalizumab is an approved drug used for IgE-mediated moderate-to-severe asthma that is refractory to high-dose inhaled corticosteroids and long-acting beta\textsubscript{2} agonist [11]. In addition, omalizumab is not indicated for the relief of acute bronchospasm or status asthmaticus [12].

We report a case of severe asthma refractory to conventional and rescue therapies in a pediatric patient, in whom omalizumab was effectively used to revert the life-threatening condition.

**Patient information**

A 17-year-old boy with a history of allergic asthma treated with on-demand SABA presented to our emergency department with severe acute asthma exacerbation. He had previously suffered from a few asthma attacks, requiring, in one case, hospital admission.

**Clinical findings and diagnostic assessment**

The boy presented to our ED with hypoxemic Acute Respiratory Failure (ARF) after 12 hours of asthma exacerbation managed at home with oral steroids and a salbutamol Metered-Dose Inhaler (MDI). In the ED, he received maximal high-dose nebulized salbutamol, intravenous methylprednisolone, nebulized epinephrine, intravenous magnesium sulphate and O\textsubscript{2} therapy, without any benefits. After 24 hours from the symptoms’ presentation, he was finally admitted to the ICU. On ICU admission, the patient presented with increased work of breathing (respiratory rate 35/minutes; use of inspiratory accessory muscles), inability to speak, orthopnea, and mild hypercapnia on blood gas analysis (BGA): pH 7.36, \(\text{Pa}_0\text{2}\) 92 mmHg, \(\text{paCO}_2\) 43 mmHg, and \(\text{HCO}_3\) - 24 mEq/L. Thus, Invasive Mechanical Ventilation (IMV) after Orotracheal Intubation (OTI) was performed (\(V_T\) 560 mL; RR 9 bpm; I/E 1:7; PEEP 0, Fi\(O_2\) 50%).

**Timeline and therapeutic interventions**

On day 1, immediately after OTI, severe respiratory acidosis (pH 7.27; \(\text{PaCO}_2\) 56 mmHg; \(\text{PaO}_2\) 101 mmHg; \(\text{HCO}_3\) - 26 mEq/L) was observed at BGA in combination with a high airway resistance, significant gas trapping, and a high time constant (\(\tau\)) (airway resistance 59 cm\(H_2O\)/L/s; PEEPi 12 cm \(H_2O\); \(\tau\) 17s). With the aim of facing off hypercarbia and respiratory acidosis, veno-venous ECCO\textsubscript{2}R was started [13].

Once a high flow 13.5 French dual lumen catheter (MAHURKAR \textsuperscript{™}, Covidien\textsuperscript{™}, Minneapolis, USA) was placed in the left femoral vein under ultrasound guidance, veno-venous ECCO\textsubscript{2}R was started (PrismaLung+, Baxter - Deerfield, IL), and the operational parameters of veno-venous ECCO\textsubscript{2}R were set as follows: a blood flow of 450 mL/min and a sweep gas flow of 10 L/min. Pre- and post-filter blood gas analyses showed a \(\Delta\text{CO}_2\) of 32.1 mmHg corresponding to 71.1\% of the total \(\text{CO}_2\) extraction. Systemic anticoagulation was initiated using unfractionated heparin (mean, \(1617\pm 295\) IU/h) to maintain an aPTT of \(71.1 \pm 26.8\) seconds. Bronchodilation was supported by continuous infusion of ketamine and inhaled sevoflurane.
On day 2, pH was compensated for by a slight increase in bicarbonate levels and a sensitive reduction in PaCO\textsubscript{2} levels due to ECCO\textsubscript{2}R (pH 7.37; PaCO\textsubscript{2} 48 mmHg; PaO\textsubscript{2} 102 mmHg; HCO\textsubscript{3}\textsuperscript{-} 28.6 mEq/L). I.v. theophylline and magnesium sulphate were also added. Chest radiography was performed, and pneumothorax was excluded.

On day 3, airway resistance reached its maximum value in the presence of persistent gas trapping and a high τ (airway resistance 130 cmH\textsubscript{2}O/L/s; PEEP\textsubscript{TOT} 10 cm H\textsubscript{2}O; τ 37 s). A rebound in the total IgE level was observed (2421 UI/mL). Film array respiratory panel analyses conducted on the bronchoalveolar lavage (BAL) assay excluded major infections.

On day 4, the BGA was as follows: pH, 7.37; PaCO\textsubscript{2} 59 mmHg; PaO\textsubscript{2} 70 mmHg; and HCO\textsubscript{3}\textsuperscript{-} 34 mEq/L. Bronchospasm was still clinically present with audible inspiratory and expiratory wheezing, confirmed by severe alterations in respiratory mechanics (R 125 cm H\textsubscript{2}O/L/s; PEEPi 9.2 cm H\textsubscript{2}O; τ 30.5 s).

Owing to the lack of a clinically relevant impact and the risk of renal injury induced by prolonged administration, sevoflurane was discontinued [14]. The day after, in consideration of the severe status of asthmaticus refractory to all the medications employed, an allergology specialist was consulted (AF) and the off-label administration of omalizumab was commenced. A single dose of Omalizumab 900 mg was injected subcutaneously, according to body weight and IgE level [12].

BAL was sampled before omalizumab administration for the following three days. Leukocyte count data are shown in Figure 1. The leukocyte count gradually decreased over the next 3 days. Figure 1 depicts how airway resistance decreased soon after omalizumab administration, suggesting its efficacy for clinical improvement. The reduction in white blood count (WBC) in BAL fluid supports this hypothesis (Figure 1). The patient’s respiratory condition progressively improved within 2 days of omalizumab administration; therefore, theophylline and magnesium sulphate were discontinued.

On day 7, as mechanical measurements improved (R 21 cm H\textsubscript{2}O/L/s; PEEPi 2 cm H\textsubscript{2}O; τ 6.5 s), RR increased to 12 bpm, while maintaining a good gas exchange (pH 7.41, PaCO\textsubscript{2} 48 mmHg, PaO\textsubscript{2} 73 mmHg, HCO\textsubscript{3}\textsuperscript{-} 31.3 mEq/L).

On day 8, due to further improvements in ventilatory mechanics, ECCO\textsubscript{2}R and ketamine were also discontinued. The ECCO\textsubscript{2}R treatment lasted 185 h, with the ECCO\textsubscript{2}R membrane cartridge replaced every 72 h. Therefore, weaning from IMV was initiated until extubation on day 9. Immediately after extubation, the patient was assisted by non-invasive ventilation (NIV) with neurally adjusted ventilatory assist (NAVA) (Servo-U, Getinge, Sölna, SW) [15,16] via an oro-nasal mask. In the absence of muscular fatigue or dyspnea, NIV was rapidly discontinued. The ECCO\textsubscript{2}R catheter was removed 24 h after spontaneous breathing, without any complications. The patient was monitored in the ICU for 72 h and then discharged to the medical ward. On day 18, the patient was discharged without any further exacerbation of in-hospital asthma.

**Outcomes and follow-up**

Asthmatic status lasted several days, and the patient remains deeply sedated, paralyzed and mechanically ventilated with continuous VV-ECCO\textsubscript{2}R in absence of complications. After extubation, he
started his new chronic therapy with a long-acting bronchodilator (beclomethasone/formoterol spray), oral montelukast, and was finally referred to a specialized center for the administration of omalizumab.

The administration of Omalizumab provided respiratory mechanic improvement and reduction of WBC in BAL.

Discussion

The humanized monoclonal anti-IgE antibody omalizumab rapidly neutralizes free IgE [17] and inhibits IgE receptor binding by steric inhibition [18]. To our knowledge, its use in acute asthma exacerbations has not been described in pediatric patients. Our clinical observations suggest that omalizumab might be useful in the critical context of refractory asthma Ig-E mediated.

Our patient did not respond to any standard medical treatment, including oxygen, inhaled SABA, inhaled short-acting muscarinic antagonists, systemic glucocorticoids, magnesium sulphate [19,20] and theophylline [21,22].

When intubation and mechanical ventilation became necessary, intravenous ketamine and inhaled sevoflurane were added as second-line therapies [4,6]. Mechanical ventilation carries the risk of serious complications due to dynamic hyperinflation, such as barotrauma and hemodynamic instability [23]. As bronchospasm is associated with prolongation of the respiratory system τ, due to expiratory flow limitation and increased flow resistance, slower emptying of alveoli may result in significant gas trapping (PEEPi) [24]. The interventions aimed at minimizing the increase in PEEPi, including a low respiratory rate with
normal or slightly increased tidal volume (HVLR high volume low-rate ventilation) and a reduced I/E ratio, were, in turn, responsible for hypercapnia and respiratory acidosis worsening [25].

The use of ECCO$_2$R allowed for the reduction of tidal volume and minute ventilation, limiting lung overinflation and gas trapping. However, we were unable to wean the patient from this supportive therapy, which cannot be applied for prolonged periods [8,26]. Off-label use of omalizumab was then considered and administered.

The reduction of symptoms, the disappearance of signs of inflammation in BAL, and the normalization of ventilation parameters occurred rapidly in the 48 hours following the introduction of omalizumab, suggesting a potential cause-effect relationship.

According to its prescribing information, Omalizumab “is not indicated for the relief of acute bronchospasm or status asthmaticus” [12]. It is also explicitly not indicated “for other allergic conditions”. Despite this, after the publication of clinical cases [27] and case series [28] indicating its efficacy, it is currently being studied as a treatment for food allergies in prospective trials [29]. This report suggests that omalizumab administration could play a role in acute asthmatic attack in a selected population.

Asthma exacerbations can be fatal. Data from the WHO Mortality Database estimated that global asthma mortality in the 5-34-year age group did not decrease appreciably from 1993 to 2006 [30,31]. Specifically, in Italy, mortality has reduced from 0.19 deaths per 100,000 people in 1993 to 0.06 per 100,000 people in 2006 [30], but in developed countries, we are now experiencing signals of upward rebound in mortality [32,33]. According to data from the US, asthma exacerbation rates among children <18 years old with current asthma decreased from 62% in 2001 to 48% in 2014 but increased in 2016 to 54% [34].

**Conclusions**

Our case suggests that the combination of ECCO$_2$R delivered via a dialysis machine and omalizumab may be an effective treatment option for status asthmaticus in the young population. In addition, these treatments can also be safely applied in secondary hospitals to avoid potentially harmful transportation, thus contributing to reduced mortality from NFA in pediatric patients.

**Acknowledgment**

The authors congratulate the ICU and dialysis teams of SS. Trinità Hospital, Borgomanero for their daily efforts and dedication to all patients.

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**Manuscript Information:** Received: March 08, 2023; Accepted: April 13, 2023; Published: April 17, 2023

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