Compassionate Use of Reslizumab in a Life-Threatening Asthma Exacerbation

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Key words: Severe asthma. Critical care. Reslizumab.

Palabras clave: Asma grave. Cuidados críticos. Reslizumab.

We present the case of a 36-year-old male, obese (IMC: 31.2kg/m^2), active smoker and heavy drinker, diagnosed with early-onset eosinophilic allergic asthma and with several hospital admissions during childhood.

He was being treated for poorly controlled asthma with, according to pharmacy refill data, low adherence to formoterol/budesonide 160/4.5mcg inhaler (2 puffs twice daily). In recent years, he had suffered several episodes of exacerbation and visits to the Emergency Room(ER) without admission.

In 2021, he was admitted to the Intensive Care Unit (ICU) due to a severe asthma exacerbation without requiring invasive mechanical ventilation(IMV). In the following months, asthma control did not improve and the patient was admitted to the Pneumology Department due to severe bronchospasm related to SARS-CoV-2 infection and discontinuation of inhalation therapy two days before admission with no evidence of pneumonia. At that time, the patient had received the first COVID-19 vaccine dose. No specific therapy was administered. Given the severe airflow obstruction (FVC:61%; FEV1:36%; FEV1/FVC:48%) and diagnosis of uncontrolled severe asthma, he was referred to the severe asthma unit for follow up.

In April 2022, he returned to the ER with an asthmatic exacerbation, without a clear trigger, reporting good adherence to previous inhaled therapy without improvement.

The patient was transferred to the ICU, where he underwent endotracheal intubation and IMV after high flow nasal cannula, high doses of intravenous methylprednisolone and hydrocortisone, salbutamol, ipratropium, magnesium sulfate and Heliox failure.

doi: 10.18176/jiaci.0920

During first day on IMV, airway resistance remained persistently high and it was decided to initiate extracorporeal CO_2 removal ($ECCO_2R$) therapy the following day.

In spite of $ECCO_2R$ just partial improve was seen and an oxygenation impairment was evident 48 hours later, so it was agreed to switch to veno-venous femoro-yugular extracorporeal membrane oxygenation (VV-ECMO) on 4th day. Fibrobronchoscopy and chest computed tomography revealed mucus plugging and atelectasis worsening his severe bronchoconstriction. Due to poor clinical evolution despite treatment and the markedly elevated eosinophilia previously recorded in his clinical history, with maximum values reaching 830/μL, on 12th day of his ICU admission, montelukast was introduced and the hospital's multidisciplinary asthma team recommended compassionate use of a single dose of reslizumab.

Improvement in mechanic respiratory parameters and consequently in ventilation and oxygenation was observed within two days from reslizumab administration and VV-ECMO was removed after 10 days of implementation. The next day his respiratory function worsened; respiratory infection was initially suspected due to fever, leucocytosis, elevated serum procalcitonine level and bilateral infiltrate in chest-X-ray. Empirical treatment with broad-spectrum antibiotherapy was started.

Due to the slow evolution, which might be explained by this complication, percutaneous tracheostomy was performed on day 23 of the IMV. Intravenous salbutamol perfusion was started on day 16 and continued until day 24. Throughout admission, the patient was treated with aerosols of salbutamol and ipratropium bromide, inhaled budesonide and intravenous methylprednisolone. On day 39, second dose of reslizumab was provided. The patient was decannulated on day 40 of ICU stay and transferred to the ward on day 42. A summary of the whole evolution is shown in Table 1 (Supplementary file).

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The patient's respiratory condition improved significantly without asthma exacerbations during the ward stay, which allowed asthma treatment reduction and medical discharge two months after admission.

Given the diagnosis of the T2 asthma phenotype and his good evolution, it was decided to schedule monthly treatment with reslizumab [1]. Two and five months of hospital discharge spirometry showed FEV1: 2.470ml (62%) and FEV1: 2.410ml (61%), respectively.

We cannot be certain that the patient would not have recovered without reslizumab or whether the transient worsening after ECMO withdrawal represented a reslizumab failure or it was due to a systemic inflammatory response syndrome (SIRS) related to ECMO decannulation. However, it should be noted that he had not responded to a previous aggressive therapeutic strategy.

Bourdin et al [2] have previously suggested the potential benefits of T2-targeted monoclonal antibodies(mAbs) as candidate drugs for a faster resolution of ICU-admitted asthma exacerbations. The compassionate use of anti-IL-5 in near-fatal asthma exacerbations has been underlined in a case reported by Pérez de Llano et al[3], where subcutaneous benralizumab was used in a patient with characteristics similar to ours, showing a complete recovery within 9 days after its administration. This effect corresponds well with the time for subcutaneous mAbs to reach maximum plasma concentration levels (6-8 days), since subcutaneous administration implies an absorption process and, consequently, shows a delay in the increase in plasma concentration as compared to intravenous administration [4]. Due to the patient's critical condition, we considered the intravenous route the most appropriate. Renner et al [5] described a case report in which the patient was successfully extubated the day after a dose of reslizumab,

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which is consistent with high initial plasma concentration after intravenously administered drugs.

Although our patient's respiratory failure improved almost immediately, he did not recover as quickly. However, it should be taken into account that after weaning from ECMO, there are many complications which might happen such as post-decannulation SIRS [6]. As it is difficult to distinguish this condition from sepsis and no microorganisms were isolated in biological samples it was treated with broad spectrum antibiotics.

Potential causes of a suboptimal response to mAbs include insufficient dosing [7]. mAbs with a soluble target, including IL-5, are expected to show increases in clearance with body weight, which could result in reduced exposure. In fact, although body weight had no impact on efficacy or eosinophil depletion; clearance and volume distribution of mepolizumab and benralizumab were higher for patients with higher BMI in clinical trials [4,8]. Mukherjee et al [9] noted that fixed-dose mepolizumab administered subcutaneously may not be as effective as intravenous reslizumab in patients with severe prednisone-dependent asthma, since with weight-based intravenous dosing more drug could reach the airway. Taken together, we hypothesized that this potential reduction in exposure could be avoided with reslizumab.

This case and those mentioned above, support that anti-IL-5 mAbs may improve the prognosis for patients with near-fatal asthma exacerbations. However, randomized clinical trials are required to determine the clinical significance of its effects in patients with refractory status asthmaticus; underlining the convenience of including obese populations.

doi: 10.18176/jiaci.0920

Conflict of interests

The author do not have any conflict of interest. This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

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