Compassionate Use of Reslizumab in a Life-threatening Asthma Exacerbation

Granda P[1], Villamañán E[2,3,4], Heinz S[1], Laorden D[3,5], Romero D[3,6], Añón JM[3,7,8], Carpio C[3,4,5], Sobrino C[2,3], Collada V[2,3], Domínguez-Ortega J[3,8], Herrero A[2,3], Quirce S[8], Álvarez-Sala R[3,4,5]

[1]Pharmacy Department, Hospital Central de la Defensa Gómez-Ulla, Madrid, Spain
[2]Pharmacy Department, Hospital Universitario La Paz, Madrid, Spain
[3]IdiPAZ, Madrid, Spain
[4]Medicine Department, Universidad Autónoma de Madrid, Spain
[5]Pulmonology Department, Hospital Universitario La Paz, Madrid, Spain
[6]Intensive Care Unit, Hospital Universitario La Paz, Instituto de Salud Carlos III, Madrid, Spain
[7]CIBERES, Instituto de Salud Carlos III, Madrid, Spain
[8]Allergy Department, Hospital Universitario La Paz, IdiPAZ, Madrid, Spain

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We present the case of an obese 36-year-old man (body mass index, 31.2 kg/m^2) who was an active smoker and a heavy drinker. He had been diagnosed with early-onset eosinophilic allergic asthma and had been admitted to hospital several times during childhood.

According to pharmacy refill data, he was being treated for poorly controlled asthma with formoterol/budesonide 160/4.5 µg (2 puffs twice daily), although adherence was poor. In recent years, he had experienced several episodes of exacerbation and had visited the emergency department; however, he was not admitted.

In 2021, the patient was admitted to the intensive care unit (ICU) owing to a severe asthma exacerbation that did not require invasive mechanical ventilation (IMV). In the following months, asthma control did not improve, and he was admitted to the pulmonology department with severe bronchospasm related to SARS-CoV-2 infection and discontinuation of inhalation therapy 2 days before admission. There was 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%; FEV_1, 36%; FEV_1/FVC, 48%) and diagnosis of uncontrolled severe asthma, the patient was referred to the severe asthma unit for follow-up.

In April 2022, the patient returned to the emergency department because of an asthma exacerbation. No clear trigger could be identified, and he reported good adherence to previous inhaled therapy, albeit without improvement.

The patient was transferred to the ICU, where he underwent endotracheal intubation and IMV after insertion of a high-flow nasal cannula. He received high doses of intravenous methylprednisolone and hydrocortisone, salbutamol, ipratropium, and magnesium sulfate, as well as heliox to prevent intubation failure.

During the 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.

The improvement with $ECCO_2R$ was only partial, and oxygenation was clearly impaired 48 hours later. Therefore, it was agreed to switch to veno-venous femoral-jugular extracorporeal membrane oxygenation (VV-ECMO) on the fourth day. Fiberoptic bronchoscopy and chest computed tomography revealed mucus plugging and atelectasis, which worsened his already severe bronchoconstriction. Given the patient's poor clinical course despite treatment and the markedly elevated eosinophilia previously recorded in his clinical history, with maximum values reaching 830/µL, montelukast was started on the 12th day of ICU admission, and the hospital's multidisciplinary asthma team recommended compassionate use of a single dose of reslizumab.

Mechanical respiratory parameters and, consequently, ventilation and oxygenation improved within 2 days of administration of reslizumab. VV-ECMO was discontinued 10 days after implementation. On the following day, respiratory function worsened, and respiratory infection was initially suspected owing to fever, leukocytosis, elevated serum procalcitonin level, and bilateral infiltrate on the chest x-ray. Empirical treatment with broad-spectrum antibiotics was started.

Given the patient's slow progress, which might be explained by this complication, percutaneous tracheostomy was performed on day 23 of IMV. Intravenous salbutamol perfusion had been 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. The second dose of reslizumab was provided on day 39. The patient was decannulated on day 40 of his ICU stay and transferred to the ward on day 42. A summary of his progress is shown in Table 1 of the Supplementary file.

The patient's respiratory condition improved significantly without asthma exacerbations during the ward stay. Asthma treatment was therefore reduced, and the patient was discharged 2 months after admission.

Given the diagnosis of the T2 asthma phenotype and the patient's good progress, it was decided to schedule monthly treatment with reslizumab [1]. Spirometry performed at 2 and 5 months after discharge revealed an FEV_1 value of 2470 mL (62%) and of 2410 mL (61%), respectively.

We cannot be certain that the patient would not have recovered without reslizumab or whether the transient worsening after withdrawal of ECMO represented a failure of reslizumab or was due to systemic inflammatory response syndrome associated with ECMO decannulation. However, it should be noted that the patient had not responded to previous aggressive therapy.

Bourdin et al [2] suggested the potential benefits of T2-targeted monoclonal antibodies (mAbs) as candidate drugs to enable faster resolution of patients with asthma exacerbations admitted to the ICU. The compassionate use

of anti–IL-5 agents in near-fatal asthma exacerbations was addressed in a case reported by Pérez de Llano et al [3], where subcutaneous benralizumab was used in a patient with characteristics similar to those of the patient we report, with complete recovery within 9 days after 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, it takes longer for the plasma concentration to be reached than with intravenous administration [4]. Given the patient's critical condition, we considered the intravenous route to be the most appropriate. Renner et al [5] reported the case of a patient who was successfully extubated the day after receiving a dose of reslizumab. This is consistent with the high initial plasma concentration observed after intravenously administered drugs.

Although the patient's respiratory failure improved almost immediately, he did not recover as quickly. However, we must remember that weaning from ECMO is followed by complications such as postdecannulation systemic inflammatory response syndrome [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.

The potential causes of suboptimal response to mAbs include insufficient dosing [7]. Clearance of mAbs with a soluble target, including IL-5, is expected to increase with body weight, thus reducing exposure. In fact, although body weight had no impact on efficacy or eosinophil depletion, clearance and volume distribution of mepolizumab and benralizumab were shown to be superior for patients with a 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 more drug could reach the airway with weight-based intravenous dosing. Taken together, we hypothesized that this potential reduction in exposure could be avoided with reslizumab.

This case and those mentioned above indicate that anti–IL-5 mAbs can improve prognosis for patients with near-fatal asthma exacerbations. However, randomized clinical trials are required to determine the clinical significance of their effects in patients with refractory status asthmaticus. Such trials should include obese patients.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Elena Villamañán
Pharmacy Department
Hospital Universitario La Paz
Paseo de la Castellana, 263
28046 Madrid, Spain
E-mail: evillabueno@telefonica.net