

# Compassionate Use of a Single Dose of Benralizumab in a Near-Fatal Asthma Exacerbation

Pérez de Llano L<sup>1</sup>, Blanco Cid N<sup>1</sup>, Ortiz Piquer M<sup>2</sup>, Dacal Rivas D<sup>1</sup>

<sup>1</sup>Pneumology Service, Hospital Lucus Augusti, Lugo, EOXI Lugo, Cervo e Monforte

<sup>2</sup>Intensive Care Unit, Hospital Lucus Augusti, Lugo, EOXI Lugo, Cervo e Monforte

## Corresponding Author

Nagore Blanco Cid

Pneumology Service. University Hospital Lucus Augusti. Lugo. Spain

Email: [naggoreich\\_soleil@hotmail.com](mailto:naggoreich_soleil@hotmail.com)

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**Palabras clave:** Asma. Benralizumab. Ataque de asma. Exacerbación del asma.

A 23-year-old man, an active smoker with occasional use of illicit drugs (cocaine and marijuana), diagnosed with early-onset allergic asthma was admitted to the respiratory care unit for a severe asthma exacerbation. His medical history included several hospital admissions during childhood (the last of them at the age of 8), positive skin prick tests to house dust mites and an average of two severe exacerbations per year. The patient acknowledged that he had stopped maintenance beclomethasone dipropionate and formoterol fumarate combination during the preceding 6-8 weeks and he had only taken albuterol many times a day. On admission, the patient's vital signs were temperature 37.3 °C, blood pressure 130/65, pulse 98 beats/min and 40 breaths/min. Hemocultures and antigen tests in detection of *Streptococcus pneumoniae* and *Legionella pneumophila* in urine negative. Polymerase chain reaction determination of buccal swab for influenza A, B and respiratory syncytial virus was negative. Blood arterial gas analysis revealed hypercapnia (PaCO<sub>2</sub> 6.9 KPa; 52 mmHg), blood eosinophilia was observed (600 cells/μL) whereas C-reactive protein and procalcitonin were within the normal interval. Toxicologic tests for illicit drugs were negative. Initial treatment included supplemental oxygen, short-acting beta-2 agonists and intravenous (IV) methylprednisolone (40 mg/6 hours). Despite these treatments, the patient's clinical condition deteriorated, and IV magnesium and IV aminophylline were added to this regimen. However, the patient developed respiratory acidosis (PaCO<sub>2</sub> 52 and pH 7.27), was transferred to the Intensive Care Unit (ICU) and required orotracheal intubation and mechanical ventilation the day after admission.

Mechanical ventilation and intensive therapy with the afore-mentioned medications did not improve the respiratory situation (Figure 1). Because of the persistent critical clinical status and the eosinophilia found at admission, we decided to administer 30 mg Benralizumab subcutaneously (SC) on the fourth day of ICU admission. Because the patient was unconscious, informed consent was obtained from his mother. The respiratory condition improved considerably four days after administering benralizumab, with pH normalization and decrease of peak inspiratory pressure and airway resistance (Figure 1). The patient was extubated on ICU day 13<sup>th</sup>, 9 days after benralizumab injection and recovered completely. The methylprednisolone dose was progressively reduced from 4<sup>th</sup> day after benralizumab injection until the day 16 and the patient was discharged 25 days after admission.

As far as we know, this is the first published case of compassionate use of benralizumab, an anti-IL-5R $\alpha$  humanized IgG1 $\kappa$  monoclonal antibody [1], in a patient who needed mechanical ventilation because of a near-fatal asthma attack, maybe due to regular medication non-adherence and albuterol overuse [2]. It must be acknowledged that we cannot assert that the benralizumab administered was responsible for the favorable clinical outcome and that the patient would have made a full recovery with just short-acting beta-2 agonists and systemic corticosteroids. Indeed, the duration of mechanical ventilation (13 days) was not different to the reported one [3]. Nevertheless, it should be taken into account that the patient had not responded to a previous aggressive therapeutic approach.

The biology of life-threatening asthma attacks remains to be fully elucidated, but it has been published that eosinophils present a widespread distribution within the respiratory tract in fatal cases whereas neutrophils can participate in special situations such as sudden-onset fatal asthma, mainly locating in the small airways [4]. Our patient had a

“T2-high” asthma phenotype (allergic, early-onset, eosinophilic asthma), but he did not respond to high doses of corticosteroids. This might be explained by a shift in the inflammatory underlying process towards a neutrophil-dominant condition and/or by the presence of eosinophilic inflammation with relative insensitivity to corticosteroids, a condition that has been found in about 25% of poorly controlled asthmatics after a 7-12 days course of oral prednisolone of 30 mg/d [5].

We chose benralizumab because it has been shown to reduce prednisolone dose in long term uncontrolled asthma [6] and because we hypothesized that an ongoing eosinophilic inflammation could have been present at the airways despite complete suppression of blood eosinophils after systemic corticosteroid therapy. On the other hand, Laviolette et al observed that peripheral blood eosinophil counts were less than the level of detection by 1 day after administration of SC benralizumab and remained depleted through the 84 days of the study and, although these authors employed doses (100 and 200 mg) above those that are used clinically (30 mg) and the significant decrease in the percentage of sputum eosinophils (from 4.6% to 0.6%) was reported at day 28, the biological effects seem to occur early on with this drug [7]. In fact, a patient with a severe asthma attack in whom systemic corticosteroids were contraindicated achieved clinically and functional significant improvement within 19 hours after SC injection of benralizumab 30 mg [8]. Besides, Tello et al published a case report on a patient who suffered a life-threatening exacerbation and improved considerably after two days of one dose of SC mepolizumab [9]. Monoclonal antibodies (mAbs) are high molecular weight compounds, and for mAbs administered via the SC route, absorption into the systemic circulation first requires transport of the drug through the interstitial space into the lymphatic system. Thus, absorption of mAbs after SC administration is a slow process, with an average time to peak concentration (T<sub>max</sub>) of 6–8 days [10], which nicely fits

with the time period our patient started to show an improvement in his medical condition (4 days) and makes it difficult to understand the rapid response to benralizumab described by Ramakrishnan et al [9].

Taking together, these case reports underline the need for a more comprehensive knowledge of mAbs pharmacokinetics in the setting of severe asthma. However, in any case, they open a window of opportunity for the treatment of life-threatening eosinophilic asthma attacks.

### **Conflict of interests**

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## Figure 1. Blood gas values and respiratory mechanics before and after benralizumab administration

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Variables	Days before and after Benralizumab administration											
	-4	-3	-2	-1	0	+1	+2	+3	+4	+5	+6	+7
pH	7,29	7,31	7,32	7,37	7,37	7,31	7,35	7,32	7,34	7,34	7,41	7,45
PaCO <sub>2</sub>	52	61	70,3	61,5	72,5	82,1	78,8	83,6	75,8	63,7	53,6	42,6
PaO <sub>2</sub>	46,5	99,5	103	69,2	61,4	59	52,8	98,8	93,6	158	76,2	93
FiO <sub>2</sub> (%)	50	39	34	34	39	43	42	46	44	39	39	43
TV (mL)	536	442	484	512	466	507	500	531	615	722	816	585
MV (L/min)	12,3	10,5	11,4	12,2	10,5	9,6	7,3	9,2	9,9	10,4	9,7	11,7
PIP (cm H <sub>2</sub> O)	41	35	36	35	30	29	41	36	24	22	25	23
mAWP (cmH <sub>2</sub> O)	15	15	18	17	11	13	18	18	12	13	17	14
PEEP (cm H <sub>2</sub> O)	6	6	10	9	1	6	12	10	5	10	10	8
Raw (cm H <sub>2</sub> O/L/sg)	126,83	114,28	94,73	88,52	108,57	100	189,04	117,39	72,72	51,92	49,48	46,15
Eosinophils (cells/ $\mu$ L)	600	100	0	0	0	0	0	0	0	0	0	0

### Footnote:

pH: Negative log of the hydrogen ion concentration; PCO<sub>2</sub>: Partial pressure of carbon dioxide (mm Hg); pO<sub>2</sub>: partial pressure of oxygen (mm Hg); FiO<sub>2</sub>: Fraction of inspired oxygen (%); TV: Tidal volume (ml); MV: Minute ventilation (L/min); PIP: peak inspiratory pressure (cm H<sub>2</sub>O); mAWP: mean airway pressure (cm H<sub>2</sub>O); PEEP: positive end-expiratory pressure (cm H<sub>2</sub>O); Raw: airway resistance (cm H<sub>2</sub>O/L/sg).

- Green rows: relevant mechanical ventilation parameters, lung mechanical characteristics, arterial blood gas values and blood eosinophil counts.
- Yellow column: day zero, administration dose of Benralizumab.
- Amber column: 4<sup>th</sup> day after benralizumab injection when we observed improvement of mechanical ventilation measurements.