

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

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A 23-year-old male active smoker who occasionally used illicit drugs (cocaine and marijuana) and had been 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 years), positive skin prick test results for house dust mites, and an average of 2 severe exacerbations per year. The patient acknowledged that he had stopped maintenance beclomethasone dipropionate and formoterol fumarate during the preceding 6-8 weeks and had only taken albuterol several times a day. On admission, the patient's vital signs were as follows: temperature, 37.3°C; blood pressure, 130/65; pulse, 98 bpm; respiratory rate, 40 breaths/min. Blood cultures and antigen tests for detection of *Streptococcus pneumoniae* and *Legionella pneumophila*

in urine were negative. Polymerase chain reaction (buccal swab) for influenza A, influenza B, and respiratory syncytial virus was negative. Blood arterial gas analysis revealed hypercapnia (PaCO₂, 6.9 mmHg; blood pressure, 52 mmHg), and the blood eosinophil count was 600/μL. Values for C-reactive protein and procalcitonin were normal. Toxicology testing for illicit drugs was negative. Initial treatment included supplemental oxygen, short-acting β₂ agonists, and intravenous methylprednisolone (40 mg/6 h). Despite these treatments, the patient's clinical condition deteriorated, and intravenous magnesium and intravenous aminophylline were added to this regimen. However, the patient developed respiratory acidosis (PaCO₂, 52 mmHg; pH, 7.27) and was transferred to the intensive care unit (ICU), where he underwent orotracheal intubation and mechanical ventilation the day after admission.

Mechanical ventilation and intensive therapy with the aforementioned medications did not improve his respiratory status (Table). Because of the persistent critical clinical status and the eosinophilia at admission, we decided to administer subcutaneous benralizumab 30 mg on the fourth day of ICU admission. Because the patient was unconscious, informed consent was obtained from his mother. His respiratory condition improved considerably 4 days after administration of benralizumab, with normalization of pH and decreased peak inspiratory pressure and airway resistance (Table). The patient was extubated on ICU day 13, that is, 9 days after his benralizumab injection, and recovered completely. The methylprednisolone dose was tapered from day 4 after the injection until 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 the anti-IL-5Rα humanized IgG1κ monoclonal antibody benralizumab [1] in a patient who needed mechanical ventilation because of a near-fatal asthma attack,

Table. Blood Gas Values and Respiratory Mechanics Before and After Administration of Benralizumab^a

Variables	Days Before and After 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 ₂	52	61	70.3	61.5	72.5	82.1	78.8	83.6	75.8	63.7	53.6	42.6
PaO ₂	46.5	99.5	103	69.2	61.4	59	52.8	98.8	93.6	158	76.2	93
FiO ₂ (%)	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 ₂ O)	41	35	36	35	30	29	41	36	24	22	25	23
mAWP (cm H ₂ O)	15	15	18	17	11	13	18	18	12	13	17	14
PEEP (cm H ₂ O)	6	6	10	9	1	6	12	10	5	10	10	8
Raw (cm H ₂ 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

Abbreviations: FiO₂, fraction of inspired oxygen; mAWP, mean airway pressure; MV, minute ventilation; PCO₂, indicates partial pressure of carbon dioxide; PEEP, positive end-expiratory pressure; PIP, peak inspiratory pressure; pO₂, partial pressure of oxygen; Raw, airway resistance; TV, tidal volume.
^aGreen rows: relevant mechanical ventilation parameters, lung mechanical characteristics, and arterial blood gas values. Yellow column: day zero, administration of dose of benralizumab. Amber column: day 4 after benralizumab injection when we observed improvement in mechanical ventilation measurements.

maybe due to nonadherence to regular medication and overuse of albuterol [2]. 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 only short-acting β_2 agonists and systemic corticosteroids. Indeed, the duration of mechanical ventilation (13 days) did not differ from values reported elsewhere [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 unclear, although eosinophils present a widespread distribution within the respiratory tract in fatal cases whereas neutrophils can participate in specific situations, such as sudden-onset fatal asthma, mainly affecting the small airways [4]. In the present case, the 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 underlying inflammatory process, which seemed to be neutrophil-dominant, 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 7-12 days taking oral prednisolone 30 mg/d [5].

We chose benralizumab because it has enabled the prednisolone dose to be reduced in chronic uncontrolled asthma [6] and because we hypothesized that an ongoing eosinophilic inflammation could have been present in the airways despite complete suppression of blood eosinophils after systemic corticosteroid therapy. On the other hand, Laviolette et al [7] observed that peripheral blood eosinophil counts were undetectable at 1 day after administration of subcutaneous benralizumab and remained depleted throughout the 84 days of the study. While these authors administered doses (100 and 200 mg) above those that are used in clinical practice (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. In fact, a patient with a severe asthma attack in whom systemic corticosteroids were contraindicated achieved significant clinical and functional improvement within 19 hours after subcutaneous injection of benralizumab 30 mg [8]. Besides, Tello et al [9] reported the case of a patient who experienced a life-threatening exacerbation and improved considerably 2 days after a single dose of subcutaneous mepolizumab. Monoclonal antibodies (mAbs) are high-molecular-weight compounds, and for those administered subcutaneously, absorption into the systemic circulation first requires transport of the drug through the interstitial space into the lymphatic system. Thus, absorption of mAbs after subcutaneous administration is a slow process, with an average time to peak concentration (T_{max}) of 6-8 days [10], which fits nicely with the time period the patient in the present case 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].

Taken together, both our case and the others discussed here underline the need for a more comprehensive knowledge of the pharmacokinetics of mAbs in the setting

of severe asthma. However, they do open a window of opportunity for the treatment of life-threatening eosinophilic asthma attacks.

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Conflicts of Interest

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