

Clinical Communications

Eosinophilic granulomatosis with polyangiitis evolution during severe eosinophilic asthma treatment with benralizumab

Alojzija Hočevar, MD, PhD^{a,b}, Peter Kopač, MD^{b,c}, Žiga Rotar, MD^{a,b}, Martina Plešivčnik Novljan, MD, PhD^{a,b}, and Sabina Škrjat, MD, PhD^{b,c}

Clinical Implications

- IL-5 blockade is an effective treatment for severe eosinophilic asthma, and first studies showed promising results also in eosinophilic granulomatosis with polyangiitis (EGPA). Nevertheless, we report 2 cases of EGPA developing shortly after the introduction of benralizumab for severe asthma.

Eosinophilic granulomatosis with polyangiitis (EGPA) is a rare small vessel necrotizing vasculitis associated with asthma and eosinophilia.¹ Eosinophils seem to play a central role in EGPA pathogenesis, and their inhibition represents an attractive treatment option.² Indeed, the monoclonal antibody mepolizumab has been recently approved by the Food and Drug Administration as the first IL-5 pathway blocking agent in EGPA.³ Benralizumab is another IL-5 blocking agent. As a monoclonal antibody against the IL-5 receptor, benralizumab enhances eosinophil apoptosis. Although benralizumab has shown efficacy for the treatment of severe eosinophilic asthma,⁴ it has not been widely studied in EGPA. A randomized control trial is underway,⁵ and currently, there is a single description of the positive, steroid-sparing effect of benralizumab along with the decrease in antineutrophil cytoplasmic antibody (ANCA) in 1 patient with EGPA.⁶ Herein, we report 2 cases of new EGPA onset, shortly after the prescription of benralizumab for severe eosinophilic asthma, highlighting that treatment outcomes cannot be uniformly predicted in asthma or EGPA.

A 28-year-old man with a 2-year history of eosinophilic asthma and the need for oral corticosteroids (OCS) 3 times per year required a maintenance treatment with 8 mg methylprednisolone daily from July 2019. In October 2019, he began treatment with 30 mg benralizumab, with significant improvement in asthma control and discontinuation of OCS in December 2019. The pulmonary function test results and the clinical and laboratory features before treatment with benralizumab are summarized in Table I. In the 36th week of benralizumab treatment, the patient was admitted to the rheumatologic department (in May 2019) with a 2-week history of low-grade fever (up to 37.6°C), arthralgia and arthritis, productive cough with haemoptysis, respiratory insufficiency, and necrotic skin purpura on the legs. Laboratory investigations revealed high inflammatory activity (erythrocyte sedimentation rate [ESR]) of 15 mm/h, C reactive protein (CRP) level of 67 mg/L (ref. 0-5), that eosinophils increased in 1 day from $0.17 \times 10^9/L$ to

$1.31 \times 10^9/L$ (ref. 0.02-0.67), and the presence of ANCAs against myeloperoxidase. Both renal function and native urine analysis were normal. Skin biopsy was performed and showed pauci-immune necrotizing vasculitis. On the lung high resolution computer tomography, mostly peribronchial distributed areas of parenchymal consolidation were observed with ground-glass attenuation, bronchial wall thickening, and mucus plugs. Electromyography (EMG) was normal, and there were no signs of heart involvement. The diagnosis of EGPA was established (baseline Birmingham Vasculitis Activity Score—version 3 [BVAS-3] was 12), benralizumab was discontinued, and treatment with cyclophosphamide (1000 mg, 2 i.v. pulses), rituximab (2×1000 mg), and high-dose glucocorticoids (1 mg/body weight prednisone equivalent) was started, with gradual clinical improvement. At the last follow-up visit in December 2019, the patient felt well, EGPA and asthma were controlled (BVAS-3, 0), and ANCA was negative while on maintenance treatment with rituximab and glucocorticoids.

A 58-year-old woman with a 20-year history of severe eosinophilic asthma with chronic rhinosinusitis and secondary adrenal insufficiency was treated with 30 mg benralizumab from July 2019 to November 2019 with significant improvement in asthma control and no more need for bursts oral glucocorticoid therapy. The pulmonary function test results and the clinical and laboratory features before treatment with benralizumab are summarized in Table I. In the 24th week of benralizumab treatment (in December 2019), she was admitted to the rheumatological department with a 3-week history of constitutional symptoms (fever up to 38.0°C, fatigue, and myalgia), generalized necrotic skin lesions, exertional dyspnoea, and oral and nasal ulcers with bloody discharge. On presentation, she had increased inflammatory parameters (ESR of 55 mm/h, CRP level of 37 mg/L) and normal eosinophils of $0.18 \times 10^9/L$ (which increased in the following 10 days to $1.41 \times 10^9/L$). Renal function and urine analysis were normal. ANCA was negative. Granulomatous lesions were seen on the nasal mucosa, and sinusitis was described on X-ray. The skin biopsy showed leukocytoclastic necrotizing vasculitis. Although the results of the pulmonary function test were normal, nodular and ground-glass interstitial changes were observed on lung high resolution computer tomography. EMG and echocardiography were normal. The diagnosis of EGPA was made (baseline BVAS-3, 19), benralizumab was discontinued, and treatment with 150 mg qd azathioprine combined with high-dose glucocorticoids (1 mg/body weight prednisone equivalent) was started, with rapid clinical improvement. At the last follow-up visit in February 2020, the patient was clinically stable with no new skin/mucous lesions, good asthma control, and a normal pulmonary function test (BVAS-3, 0).

The treatment of severe asthma with anti-IL-5 inhibition represents a clinical challenge and might have an unpredicted response due to complex pathogenetic mechanisms. Asthma with eosinophilia is a distinctive pulmolologic entity but is also part of the eosinophilic phase of EGPA. It is possible that in the period before treatment with benralizumab, both our patients were already in the eosinophilic phase of EGPA that was masked with

TABLE I. Pulmonary function test results and clinical and laboratory features of patients before treatment with benralizumab

	Patient 1	Patient 2
FEV ₁	2590 mL (55%)	1870 (86%)
FVC	5090 mL (90%)	2950 (109%)
eNO (ppb)	>100	>100
DLCO %	88	114
FEV ₁ /FVC	50	63
Inhaled budesonide dosing (μg/day)	960	1200
Oral methylprednisolone (mg/day)	8	0
No. of asthma exacerbations/year with OCS treatment	3	4
Peripheral eosinophilia (cells/μL)	350	700
Allergen sensitization	House dust mites	—
Upper airway disease	Chronic rhinosinusitis	Chronic rhinosinusitis
Major finding on high-resolution computed tomography	Moderate bronchial wall thickening	Bronchial wall thickening, mucus plugs, bronchiectasis
Other organ/system involvement	No	No
Total IgE (IU/mL)	670	2000
ANCA	1:20 (MPO = 19 E/mL, PR3 < 10 E/mL)	Neg

ANCA, Antineutrophil cytoplasmic antibodies; *DLCO* %, diffusion capacity; *eNO*, nitric oxide in exhaled air; *FEV₁*, forced expiratory volume in 1 second; *FVC*, forced vital capacity; *MPO*, myeloperoxidase; *OCS*, oral corticosteroids; *PR3*, proteinase 3.

the daily or frequent use of low-dose OCS due to symptoms of uncontrolled asthma. During tapering and discontinuation of OCS after treatment with the anti-IL-5 agent, EGPA could have evolved into a clinically overt vasculitic phase. This mechanism is most likely to cause EGPA in asthmatic patients and is probably also responsible for the EGPA development in these 2 cases.

We believe that the treatment with 30 mg benralizumab was successful in controlling severe asthma, as the patient managed to discontinue OCS. Despite some evidence showing a decrease of myeloperoxidase-ANCA and elimination of eosinophils in first 112 days after 30 mg benralizumab introduction in patient with EGPA,⁶ this dose seems to be insufficient for preventing the evolution to EGPA from the initial eosinophilic phase of the disease in our patients. Likewise, mepolizumab has been approved as a successful IL-5 pathway blocking agent in EGPA at higher doses compared with the dosing for severe asthma.^{3,6}

Benralizumab treatment enhances eosinophil apoptosis, and we therefore expected negligible serum concentrations for patients on benralizumab or at least stable low values, because the blood eosinophils are not universally suppressed by beralizumab and may be detected even in those without known EGPA.⁴

However, not only persistent mild peripheral eosinophilia was seen in both our patients, there was even a clear simultaneous trend in increasing the level of peripheral eosinophilia despite benralizumab treatment in first weeks after the introduction of the Q8 treatment interval. One could hypothesize that these findings might be predictors of future EGPA evolution. Additional data are urgently needed to confirm this clinical observation.

^aDepartment of Rheumatology, University Medical Centre Ljubljana, Ljubljana, Slovenia

^bFaculty of Medicine, University of Ljubljana, Ljubljana, Slovenia

^cUniversity Clinic of Respiratory and Allergic Diseases Golnik, Golnik, Slovenia
No funding was received for this work.

Conflicts of interest: P. Kopac reports receiving fees for lectures, advisory boards organized by AstraZeneca, Teva, and GSK, but not linked to the content of this letter. S. Škrat reports receiving fees for lectures, advisory boards organized by Novartis, AstraZeneca, Chiesi, Teva, and GSK, but not linked to the content of this letter. The rest of the authors declare that they have no relevant conflicts of interest.

Received for publication March 2, 2020; revised March 24, 2020; accepted for publication April 2, 2020.

Available online ■ ■

Corresponding author: Sabina Škrat, MD, PhD, University Clinic of Respiratory and Allergic Diseases Golnik, Golnik 36, 4204 Golnik, Slovenia. E-mail: sabina.skrat@klinika-golnik.si.

2213-2198

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<https://doi.org/10.1016/j.jaip.2020.04.006>

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