

Clinical Communications

Benralizumab as a glucocorticoid-sparing treatment option for severe asthma in eosinophilic granulomatosis with polyangiitis

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Clinical Implications

- Benralizumab has proven to be a promising treatment option in severe/refractory eosinophilic granulomatosis with polyangiitis eosinophilic asthma. Twenty-four-week benralizumab treatment reduced significantly the intake of glucocorticoids and improved clinical manifestations and patient-reported outcomes.

Eosinophilic granulomatosis with polyangiitis (EGPA) is a rare multisystem disease characterized by small-vessel vasculitis, asthma, sinusitis, and blood and tissue eosinophilia, usually associated with the presence of antineutrophil cytoplasmic antibodies (ANCA) in 30% to 40% of the cases.¹ Asthma typically antedates onset of systemic disease and may develop in a severe glucocorticoid-dependent phenotype. More than 70% of patients also suffer sinonasal disease, such as chronic rhinosinusitis with nasal polyposis.² Glucocorticoids are the cornerstone of EGPA management, with or without immunosuppressive agents. However, most patients may need long-term glucocorticoid maintenance treatment to control asthma and chronic rhinosinusitis with nasal polyposis, with a significant drug-related morbidity.³ IL-5 is a critical cytokine for priming, proliferation, and migration of eosinophils,⁴ and its inhibition with neutralizing mAbs, such as mepolizumab, proved effective in prolonging EGPA remission and reducing the requirement for glucocorticoids.⁵ Unfortunately, up to 47% of patients with EGPA treated with high-dose mepolizumab did not achieve protocol-defined remission and on treatment cessation, disease manifestations recurred.⁵ Benralizumab is an mAb that binds IL-5 receptor, thus neutralizing eosinophils via antibody-dependent cellular cytotoxicity, and currently has been approved for the treatment of severe eosinophilic asthma.⁶ To date, only 2 case reports describing the efficacy of benralizumab in EGPA have been published: one demonstrated a decrease in myeloperoxidase-ANCA,⁷ and the other proved the efficacy of benralizumab in the treatment of eosinophilic myocarditis.⁸ Here, we describe clinical features and patient-reported outcomes in a series of refractory and glucocorticoid-dependent patients with asthma with EGPA, treated with benralizumab.

Patients with established EGPA (fulfilling the American College of Rheumatology criteria) and severe relapsing or refractory (at least 2 exacerbations while on high-dose inhaled

steroids and long-acting β_2 -agonists in the previous year or recurrence of symptoms upon tapering of glucocorticoids at any dose > 7.5 mg/d requiring continuous treatment) eosinophilic asthma were commenced on benralizumab 30 mg administered by subcutaneous injections (every 8 weeks after the initial 3 doses given every 4 weeks). All patients were followed in a multidisciplinary setting, by pulmonary, otorhinolaryngology, and rheumatology physicians. Glucocorticoid doses were reviewed during each consultation and adjusted if deemed appropriate.

Clinical data including the dose of glucocorticoids, organ involvement, Birmingham vasculitis activity score, lung function (FEV₁, forced vital capacity, and forced expiratory flow at 25%-75%), fractional exhaled nitric oxide, and need for hospitalization were recorded at baseline and after 24 weeks of treatment. Change from baseline in patient-reported outcome was assessed for the Asthma Control Questionnaire 5-item version, the Asthma Control Test, the Asthma Quality of Life Questionnaire, and the Sino-Nasal Outcome Test-22.

Data are expressed as median and interquartile ranges. Mann-Whitney *U* test was used to compare the differences for nonparametric variables. A 2-tailed *P* value of less than .05 was considered significant. Written informed consent was obtained from all patients.

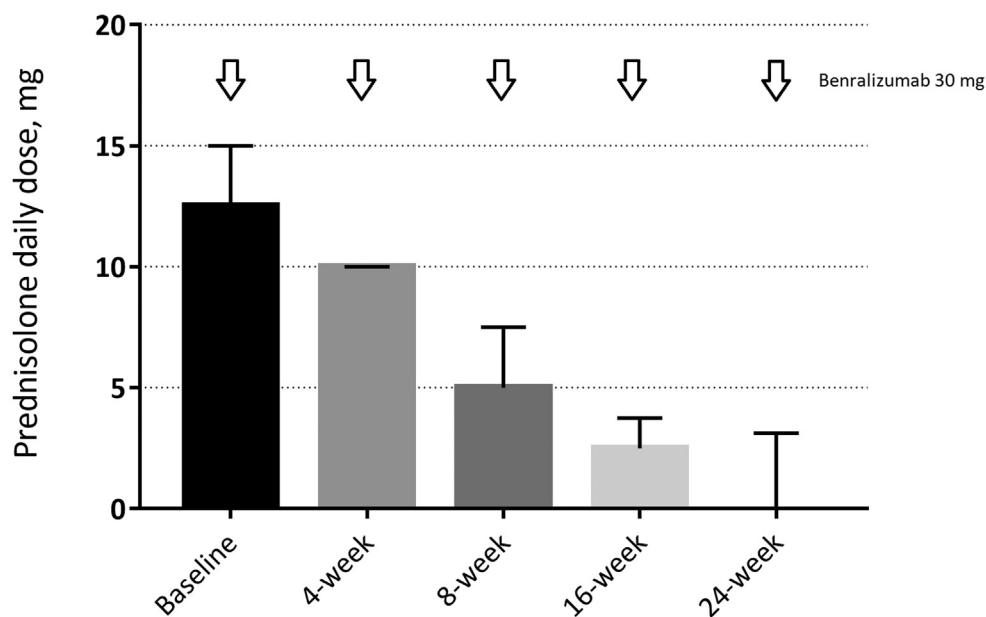
Five patients with EGPA were included between July and October 2019. They were middle-aged (42 [32.5-55.5] years), 4 of 5 were female, all were white, and had a long-standing disease (20 [16-23.5] months). ANCA-myeloperoxidase positivity rate (20%) was in keeping with previously described EGPA cohort. All patients had adult-onset asthma and paranasal sinus involvement, 1 of 5 had peripheral neuropathy, and no cardiac or cutaneous involvement was reported. At baseline, median eosinophil count was 1200/ μ L, c-reactive protein level was 2.5 mg/L, and Birmingham vasculitis activity score was 4 (see Table E1 in this article's Online Repository at www.jaci-inpractice.org). None of the patients was tested for platelet-derived growth factor receptor rearrangements or KIT, JAK2, or BCR-ABL1 mutations.

At benralizumab commencement, all patients were receiving a daily oral glucocorticoid dose above 10 mg. Three patients had received methotrexate therapy, 1 mycophenolate and 1 azathioprine. Three patients failed mepolizumab therapy in the previous 6 months (see Table E2 in this article's Online Repository at www.jaci-inpractice.org).

Despite ongoing therapy, all patients were suffering from severe and relapsing asthma with multiple asthma attacks in the last month, needing an increase of more than 30% in the oral prednisone dose for those on regular prednisone therapy (3 [2.5-4.5] episodes) or requiring multiple oral/parenteral glucocorticoid courses in those not on regular glucocorticoid treatment (2 [1.5-3.5] courses).

Benralizumab was well tolerated and there were no adverse events.

After 24 weeks of treatment, we observed a significant reduction in oral glucocorticoid intake, from median daily prednisolone dose of 12.5 (11.25-15) mg to 0 (0-3.12) mg (*P* = .01) (Figure 1). Notably, 3 of 5 patients were able to completely withdraw glucocorticoids. Alongside, a complete depletion in circulating eosinophils was observed in all patients (*P* = .01).



Eos, cells/ μ L	1200 [555-1495]	0 [0-0]	$p=0.01$
CRP, mg/L	2.5 [1.7-3.9]	2.45 [1.7-2.9]	ns
BVAS	4 [3-4]	0 [0-0]	$p=0.01$
FEV1	1.9 [1.39-2.29]	2.4 [2.01-3.26]	ns
FVC	2.25 [1.92-3.21]	2.86 [2.41-3.91]	ns
FEF 25-75%	1.63 [0.99-2.07]	2.79 [2.20-3.50]	ns
FeNO	61 [24-77]	26 [7-72]	ns
ACT	14 [10-17]	22[21-25]	$p=0.01$
ACQ5	19 [17-21]	4[0-7]	$p=0.01$
AQLQ	105 [97-132]	199[150-217]	$p=0.02$
SNOT22	64 [47-71]	35 [8-37]	$p=0.02$

FIGURE 1. Significant reduction in median glucocorticoid doses over the treatment period. Complete eosinophils depletion and improvement in pulmonary function alongside patient-reported outcomes were observed after 24 weeks of treatment. The arrows denote benralizumab 30-mg injections. *ACQ5*, Asthma Control Questionnaire 5-item version; *ACT*, Asthma Control Test; *AQLQ*, Asthma Quality of Life Questionnaire; *BVAS*, Birmingham vasculitis activity score; *CRP*, c-reactive protein; *Eos*, eosinophils; *FEF 25%-75%*, forced expiratory flow at 25%-75%; *FeNO*, fractional exhaled nitric oxide; *FVC*, forced vital capacity; *SNOT-22*, Sino-Nasal Outcome Test-22.

Pulmonary function tests showed a general improvement, despite not reaching statistical significance. FEV₁ increased from 1.9 (1.39-2.29) to 2.4 (2.01-3.26) L, forced vital capacity from 2.25 (1.92-3.21) to 2.86 (2.41-3.91) L, and forced expiratory flow at 25%-75% from 1.63 (0.99-2.07) to 2.79 (2.20-3.50) L/s. We observed a decrease in airway inflammation measured with fractional exhaled nitric oxide, from 61 (24-77) to 26 (7-72) parts per billion, without statistical significance.

Patient-reported outcome measures demonstrated a better disease control, with an improvement in the Asthma Control Test score (14 [10-17] vs 22 [21-25]; $P = .01$), the Asthma Control Questionnaire 5-item version score (19 [17-21] vs 4 [0-7]; $P = .01$), the Asthma Quality of Life Questionnaire score (105 [97-132] vs 199 [150-217]; $P = .02$), and the Sino-Nasal Outcome Test-22 score (64 [47-71] vs

35 [8-37]; $P = .02$). No significant changes were observed in other organ manifestations, c-reactive protein, nor ANCA status or titer. During the treatment period, no severe asthma exacerbations or need for hospitalization or infections were registered.

Asthma in patients with EGPA frequently becomes severe and rapidly glucocorticoid-dependent. Most patients may require long-term maintenance treatment with low-dose glucocorticoids to control respiratory symptoms once remission of the systemic eosinophilic disease has been obtained, thus contributing to a significant morbidity. Deep suppression of eosinophils via antibody-dependent cellular cytotoxicity might be crucial for an improved control of EGPA symptoms and could justify the efficacy of benralizumab in patients who failed mepolizumab therapy.⁹ However, the lack of improvement in c-reactive protein or ANCA status and

the inclusion of a cohort with a persistent asthma EGPA phenotype does not allow us to investigate the treatment efficacy on extrapulmonary, vasculitic disease phenotype.

Although data were prospectively collected, the present study was not a clinical trial and it may consequently be subjected to bias. Moreover, our follow-up might be short, but it is in keeping with the 24-week primary end point of the mepolizumab trial.⁵

In conclusion, benralizumab has proven to be a promising treatment option in severe/refractory EGPA asthma. Twenty-four-week treatment reduced significantly the intake of glucocorticoids and improved clinical manifestations and patient-reported outcomes, even in mepolizumab nonresponder patients.

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TABLE E1. Ongoing clinical features of patients with EGPA at benralizumab commencement

Patient no.	Age (y)	Sex	Disease duration (mo)	ANCA-MPO (KIU/L)	BVAS v3	VDI	CRP (mg/L)	Eosinophils (cells/ μ L)	Organ involvement	Daily prednisone dose (mg)
1	55	Female	25	Negative	4	2	3	560	Asthma, ENT	15
2	32	Female	20	Negative	4	2	2	1600	Asthma, ENT, pulmonary infiltrates, arthralgia	10
3	56	Female	19	84	2	1	1.6	550	Asthma, ENT, pulmonary infiltrates, peripheral neuropathy	15
4	42	Female	13	Negative	4	1	4.2	1390	Asthma, ENT, pulmonary infiltrates	12.5
5	33	Male	22	Negative	4	2	2.9	1200	Asthma, ENT, arthralgia, fever	12.5

ANCA, Antineutrophil cytoplasmic antibody; BVASv3, Birmingham vasculitis activity score, version 3; CRP, c-reactive protein; EGPA, eosinophilic granulomatosis with polyangiitis; ENT, ear, nose, and throat; MPO, myeloperoxidase; VDI, vasculitis damage index.

TABLE E2. Clinical features of the mepolizumab nonresponder patients

Patient no.	Age at MEPO administration (y)	Sex	Disease duration at MEPO administration (mo)	ANCA-MPO (KIU/L)	BVAS v3 at MEPO administration	MEPO dosage (mg)	MEPO treatment duration until failure (mo)	Eosinophils at MEPO administration (cells/ μ L)	Eosinophils at MEPO failure (cells/ μ L)	Daily prednisone dose at MEPO failure (mg)	Long-acting β -agonists and/or inhaled steroids at MEPO failure
1	53	Female	25	Negative	4	300	16	1350	1000	10	Formeterol
2	30	Female	20	Negative	4	300	19	3000	1200	5	Budesonide/formeterol
4	40	Female	13	Negative	4	100 for 5 mo, then increased to 300	18	1500	150	15	Fluticasone/salmeterol

ANCA, Antineutrophil cytoplasmic antibody; BVASv3, Birmingham vasculitis activity score, version 3; MEPO, mepolizumab; MPO, myeloperoxidase.

Patients' numbering refers to [Table E1](#). Treatment failure was defined as the reoccurrence of multiple asthma attacks (at least 3 episodes in the last 3 mo), needing an increase of >30% in oral prednisone dose for those who were on a regular prednisone therapy or requiring oral/parenteral glucocorticoid courses for those not on regular prednisone.