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Ismael Carrillo-Martin, MD, Andy Abril, MD, Angela M. Donaldson, MD, Alexei Gonzalez-Estrada, MD



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Title: An alternative approach against eosinophils for the treatment of eosinophilic granulomatosis with polyangiitis

Authors: Ismael Carrillo-Martin, MD;^{1,2} Andy Abril, MD;^{1,3} Angela M Donaldson, MD⁴; Alexei Gonzalez-Estrada MD^{1,2}

¹Department of Internal Medicine, Mayo Clinic, Jacksonville, FL

²Division of Pulmonary, Allergy and Sleep Medicine, Department of Medicine, Mayo Clinic, Jacksonville, FL

³Division of Rheumatology, Department of Medicine, Mayo Clinic, Jacksonville, FL

⁴Department of Otorhinolaryngology (ENT)/Head and Neck Surgery, Mayo Clinic, Jacksonville, FL

Corresponding author:

Alexei Gonzalez-Estrada, M.D.

Division of Pulmonary, Allergy and Sleep Medicine, Department of Medicine

4500 San Pablo Road, Jacksonville, FL, 32224

Tel: 904-953-2451

Fax: 904-953-0017

Email: gonzalez.alexei@mayo.edu

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26 ***Clinical implications:*** Therapy targeting eosinophils has been shown to induce remission in
27 patients with eosinophilic granulomatosis with polyangiitis (EGPA). Targeting eosinophils
28 through different mechanisms of actions might be beneficial and could be a valuable alternative
29 in the treatment of EGPA.

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To the Editor:

Eosinophilic granulomatosis with polyangiitis (EGPA) is a systemic necrotizing vasculitis characterized by blood and tissue eosinophilia that may present as purpura, sinusitis, asthma pulmonary infiltrates, neuropathy, and renal, cardiac (e.g. coronary artery disease, pericardial effusion, peri/myocarditis, cardiomyopathy) or gastrointestinal disease (e.g. hemorrhage, infarction, pancreatitis).¹ Management of EGPA focuses on achievement and maintenance of remission (absence of clinical signs or symptoms attributable to EGPA) mainly with glucocorticoids alone or with immunosuppressants (e.g. cyclophosphamide) depending on severity of disease and end-organ involvement.¹

Given the wide array of side effects associated to these traditional therapeutic options and based on the increasing knowledge on the pathophysiology of EGPA, emerging therapies aim to induce and maintain remission while reducing exposure to glucocorticoids and immunosuppressants and their adverse effects. Mepolizumab, a humanized monoclonal antibody (mAb) against interleukin 5 (IL-5), is an FDA-approved agent for EGPA as a steroid-sparing and relapse prevention agent that reduces eosinophils proliferation and differentiation and has been shown to assist in achieving prolonged remission, reducing steroid dose and relapse frequency.²⁻⁵ The results seen so far with mepolizumab reinforce the role of eosinophils in the pathophysiology of EGPA; the question remains whether targeting IL-5 and eosinophilic proliferation and differentiation from different approaches (i.e. targeting its receptor on eosinophils) may provide similar benefits as mepolizumab in patients with EGPA. We present a case of a patient with EGPA who benefited from treatment with benralizumab, a humanized mAb against interleukin-5 receptor α -subunit (IL-5R α).

A 23-year-old previously healthy man reported new onset sinus congestion, cough and wheezing. Multiple bronchoscopies and bronchoalveolar lavages performed at outside facilities showed necrotic debris and eosinophils. Pulmonary imaging was unremarkable. His symptoms failed to respond to numerous courses of inhalers, systemic glucocorticoids and antibiotics; and surgical removal of polypoid tissue from the ethmoid and sphenoid sinuses improved his symptoms moderately although only temporarily. On June 2018, approximately 5 weeks after the onset of sinus congestion, cough and wheezing, the patient experienced rapidly increasing dyspnea and chest pain secondary to a pericardial effusion with impending tamponade requiring a pericardial window. On the basis of the patient's symptomatology and the pathological review of the pericardium reporting eosinophilic vasculitis and tissue eosinophilia, the patient was diagnosed with EGPA.

Given the rapid progression of the patient's symptoms and the severity of disease based on cardiac involvement, the decision was made to start the patient a remission-induction regimen; however, the patient had already failed to respond to glucocorticoids at an outside institution and declined starting immunosuppressants. Once the cardiac tamponade and pericarditis were treated (pericardial window, and IV corticosteroids at 1mg/kg/day), we decided to add an anti-IL-5 mAb to his long-term regime but for insurance reasons the patient was not eligible to receive mepolizumab. The patient was started on benralizumab 30 mg every four weeks alongside prednisone 40mg/day and inhaled fluticasone-furoate/vilanterol (200mcg/25mcg) once daily. The dose of prednisone was successfully tapered to 20 mg/day and 10 mg/day after eight weeks and 22 weeks respectively.

After 55 weeks on benralizumab, the patient reported 3-5 episodes of sinus and nasal congestion. While on benralizumab and the before mentioned dose of inhaled fluticasone-furoate/vilanterol,

the patient uses albuterol (90mcg) as needed approximately once a week for shortness of breath, and denies any nocturnal symptoms as well as daily activity impediments secondary to asthma symptoms. He denies other symptoms and has not presented new episodes of pericarditis, serositis or other events suggestive of active vasculitis. Laboratory findings show a depletion of eosinophils and the spirometry showed an increase in FEV1 (Table I). He denied any adverse events related to benralizumab and refers to be tolerating the new regime adequately.

Benralizumab is used in the treatment of severe, uncontrolled asthma for its oral glucocorticoid-sparing effect,⁶ and patients with EGPA might also benefit from this. Benralizumab binds to IL-5R α , attracting natural killer cells and inducing apoptosis of the eosinophil through antibody-dependent cell-mediated cytotoxicity.^{6,7} In contrast, mepolizumab reduces eosinophil proliferation and differentiation by binding to circulating IL-5 thereby preventing its interaction with its receptor on the eosinophils' surface.²⁻⁵ It has been suggested that the differences in mechanisms of action (MoA) might lead to a more intense depletion of eosinophils by benralizumab than other anti-IL-5 mAb (mepolizumab and reslizumab) on account of it being independent of IL-5 levels and insensitive to the effects of interleukin-3 and granulocyte-macrophage colony-stimulating factor.^{6,7} These features might make benralizumab an interesting option for the treatment of EGPA.

The effectiveness and safety profile of benralizumab in patients with severe, uncontrolled asthma show that patients given 30 mg every four or eight weeks of benralizumab presented significant clinical improvement and only a few -mostly non-severe- adverse events after up to two years.^{6,8} Also a case of EGPA treated with benralizumab was reported to successfully help in tapering the dose of systemic corticosteroids and showed a decrease in values of MPO-ANCA after three

98 weeks of starting therapy.⁹ After one year with benralizumab our patient remains in remission
99 and reports no adverse effects from the mAb.

100 While the exact role of eosinophils in the pathology of EGPA is still uncertain, eosinophilic
101 granulomatous inflammation, and peripheral and tissue eosinophilia suggest they are relevant.

102 Furthermore, treating patients with EGPA by blocking the effects of IL-5 in eosinophils has been
103 proven to be effective in inducing disease remission and lowering the need for glucocorticoids²⁻⁵
104 which reinforces the quintessential role of eosinophils in EGPA pathogenesis.

105 In conclusion, having alternative approaches to the same targets (eosinophils and IL-5) might
106 prove beneficial for patients with EGPA since patients' clinical responses may vary between
107 different medications with similar effects and different MoA. Future randomized controlled
108 studies are needed to assess the effects, safety, and benefits of treating EGPA patients with
109 benralizumab.

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141 Tables

Table I: Prednisone dose, laboratory and spirometry findings before and after benralizumab*		
Drug	Dose at start of benralizumab	Dose after 55 weeks on benralizumab
Prednisone	40 mg/day	10 mg/day
Test	Before benralizumab	On benralizumab ⁺
CBC with differential		
Eosinophils	2.21 x 10 ⁹ /L	0.0 x 10 ⁹ /L
Spirometry		
FEV1 (% of predicted)	84 %	91 %
ANCA	Negative	Negative
CRP	<3 mg/mL (normal ≤8 mg/mL)	<3 mg/mL (normal ≤8 mg/mL)
ESR	<1mm/1h (normal 0-22 mm/1h)	2 mm/1h (normal 0-22 mm/1h)
CBC = complete blood count; FEV1 = forced expiratory volume in one second; ANCA = Antineutrophil Cytoplasmic Antibodies; CRP = C-Reactive protein; ESR = Erythrocyte sedimentation rate		
*= benralizumab was administered at 30 mg every 4 weeks		
⁺ = after 55 weeks on benralizumab		

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