



# Benralizumab substitution monotherapy in symptomatic relapsing asthma-dominant eosinophilic granulomatosis with polyangiitis

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## Abstract

There is increasing interest in biologicals in steroid-resistant or steroid-dependent eosinophilic granulomatosis with polyangiitis (EGPA). We describe successful benralizumab monotherapy in asthma-dominant EGPA. Sixteen years ago, a 38-year-old male was diagnosed with multisystemic illness with asthma, arthralgias, Bell's palsy and nephrotic syndrome, with 20.3% eosinophilia (absolute count 1160 K/ $\mu$ L), ESR 50 mm/hour, albumin 2.3 g/dL, serum creatinine 1.1 mg/dL, slightly above baseline and negative immunology work. Kidney biopsy demonstrated diffuse podocyte foot process effacement with minimal change disease, without vasculitis and EGPA was diagnosed. He achieved early remission with corticosteroids and intravenous cyclophosphamide and was maintained on prednisone and mycophenolate mofetil. Nevertheless, he repeatedly experienced severe asthma exacerbations, falls in FEV-1% and recurrent relapsing eosinophilia. He was successfully started on benralizumab and was weaned off mycophenolate mofetil and prednisone. Eosinophilia was corrected and FEV-1% normalized. We support calls for larger trials of the biologicals in EGPA.

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## Introduction

Eosinophilic granulomatosis with polyangiitis (EGPA), a rare but potentially life-threatening inflammatory condition manifested most by asthma, upper airway inflammation, eosinophilia and small vessel vasculitis has two predominant subtypes - a predominantly eosinophilic syndrome that is anti-neutrophil cytoplasmic antibody (ANCA) negative and a small vessel granulomatous vasculitis that is ANCA positive (1). New classification criteria for EGPA are under development (2,3). The management of EGPA had traditionally involved anti-inflammatory and immunosuppressant therapy with glucocorticoids, cyclophosphamide and azathioprine. The choice of therapy depends upon clinical manifestations and disease severity. Newer therapies, namely biological drugs such as rituximab (a monoclonal antibody targeting B cells) and mepolizumab (a monoclonal antibody targeting interleukin 5, thus inhibiting eosinophils) have been reported to be effective in EGPA (4,5). Other biologicals like reslizumab (anti-

IL-5 antibody) and omalizumab (anti-IgE antibody) have been shown in small studies to be steroid-sparing in EGPA with severe asthma (6,7). Benralizumab, an anti-IL-5 receptor antibody, has demonstrated to be steroid-sparing in EGPA with asthma in two small studies that involved a total of 15 patients (8,9). Chica-Guzman et al, in late 2020, recently reported the successful substitution management of EGPA with benralizumab monotherapy in place of oral corticosteroids (10). We report our experience of substitution monotherapy with benralizumab in asthma-dominant EGPA, to replace prednisone and mycophenolate mofetil.

## Case Report

Sixteen years ago, a 38-year-old Caucasian male had complained of upper back pain, crampy abdominal pain and pain in his right shoulder blade area. Then followed numbness in his right index finger and then his right thumb and middle finger. Initial evaluation was non-diagnostic and he received analgesics without much improvement. In January 2006,



**Key point**

Recently, there is increasing interest in biologicals including anti-interleukin 5 antibodies and anti-interleukin 5 receptor antibodies in the management of steroid-resistant and/or steroid-dependent eosinophilic granulomatosis with polyangiitis (EGPA). Benralizumab, an anti-IL 5 receptor antibody, is steroid sparing. We describe the successful substitution benralizumab monotherapy in a patient with asthma-dominant EGPA who had previously experienced severe recurring asthma exacerbations with eosinophilia, despite chronic maintenance immunosuppression with prednisone and mycophenolate mofetil, together with budesonide-formoterol HFA 80-4.5, 2 puffs as directed, two times daily, and oral montelukast, 10 mg daily. He required repeated intermittent dose escalations of oral corticosteroids. His asthma has since been controlled with benralizumab monotherapy and the eosinophil count had been persistently zero.

he had a severe asthma attack with difficulty breathing, and he received prednisone for a few weeks. He subsequently developed acute left facial weakness consistent with Bell's palsy and prednisone was restarted. Concurrent urinalysis revealed 3+ dipstick proteinuria and dipstick hematuria. Urine protein creatinine ratio was 11.6 (<0.11) mg/mg. A 24-hour urine protein measurement was not completed. The patient was hypertensive (163/95 mm Hg), with 1+ bipedal edema with left-sided facial droop. Complete blood count showed hemoglobin 14.7 g/dL, platelet count 303 K/ $\mu$ L and total WBC 5.73 K/ $\mu$ L. He had 20.3% eosinophils (absolute count 1160 K/ $\mu$ L) on his differential. Erythrocyte sedimentation rate was 50 mm/h. Serum creatinine was slightly above recent baseline at 1.1 mg/dL and albumin was 2.3 g/dL. He was admitted with nephrotic syndrome and suspicion for EGPA. Immunology work-up was negative: ANA was <40 (0-40 Dils), ANCA was negative, proteinase 3 antibody was negative, myeloperoxidase antibody was negative, C3 complement was 118 (79-152) mg/dL, C4 complement was 21 (16-38) mg/dL, IgE was 72 (0-165) IU/ml and Lyme antibody was negative. Chest radiograph was normal. A kidney biopsy in February 2006 showed diffuse foot process effacement consistent with minimal change disease with no evidence for vasculitis. Head MRI showed normal brain anatomy but demonstrated pansinusitis and nasal polyps. Following these investigations, a formal diagnosis of EGPA was confirmed. Treatment of EGPA was initiated with intravenous methylprednisolone 1 g daily for three days, followed by oral prednisone taper, starting at 60 mg/daily and tapering down as tolerated over several months to 5-10 mg/d. Pneumocystis carinii pneumonia prophylaxis was initiated with three times a week double strength trimethoprim-sulfamethoxazole 800-160. Intravenous cyclophosphamide 500 mg/m<sup>2</sup> body surface area (BSA), was started, was repeated in two weeks, and then monthly for another six months with close monitoring of hematological indices. Captopril 25 mg, three times daily, was started for hypertension and nephrotic range proteinuria. Left facial weakness improved after two weeks. Eosinophilia resolved and

eosinophil count was 0.9% after three doses of intravenous methylprednisolone. Edema quickly resolved, hypertension was controlled, and serum albumin normalized at 4.3 g/dL after two months. Urine protein creatinine ratio decreased from 11.6 mg/mg to 0.07 mg/mg after two months of immunosuppression. ESR decreased down to 14 mm/h after two months of immunosuppression. He was transitioned to mycophenolate mofetil 500-1000 mg two times daily with tapered prednisone after six months of cyclophosphamide administration. He was maintained with mycophenolate mofetil and prednisone with multiple unsuccessful attempts to wean him off prednisone. He had no recurrence of proteinuria or neurological symptoms. He however continued to have recurrent rhinosinusitis and three years after the initial diagnosis of EGPA, he underwent septoplasty with functional endoscopic sinus surgery (FESS) of the ethmoid, maxillary, frontal and sphenoid sinuses in April 2009. Initially, hypertension was controlled with captopril which was later switched to daily lisinopril. He gained over 30 lb with prednisone therapy but was able to lose most of that weight some years later and for some time did not need antihypertensive therapy. Over the next ten years he continued to have difficulty weaning prednisone and mycophenolate mofetil due to intermittent symptoms of asthma and intermittently worsening joint pains especially involving the knees. The sinusitis had remained stable after the FESS procedure and the main problem in the last several years was the recurring symptomatic asthma exacerbations. These asthma exacerbations were increasingly problematic despite continued use of oral prednisone and mycophenolate mofetil, budesonide-formoterol HFA (Symbicort) 80-4.5, 2 puffs as directed, two times daily, oral montelukast tablets, 10 mg daily and budesonide (Pulmicort) 0.5 mg/2mL nebulizer suspension, to irrigate the nostrils. Eosinophil count fluctuated up and down with the asthma exacerbations, but he did respond to intermittent dose escalations of oral corticosteroids with continued mycophenolate mofetil. However, during 2017 and 2018, his asthma exacerbations had worsened in intensity and frequency. Early in 2019, his FEV-1% (FEV-1/FVC) which had mostly ranged 80%-90% had quickly dropped to 52% (Figure 1). His allergy/immunology specialist initiated benralizumab 30 mg every four weeks, in April 2019. At that time, he was on prednisone 10 mg daily and mycophenolate mofetil 750 mg twice daily. His asthma responded promptly to benralizumab. He was weaned off mycophenolate mofetil after 14 months on benralizumab. He finally came off prednisone after 16 months on benralizumab. His asthma control remained excellent on benralizumab monotherapy 30 mg every eight weeks (Figure 1). Sustained improvement in FEV-1% along with complete disappearance of eosinophils has been maintained on continued benralizumab monotherapy (Figure 2). In late 2020, losartan 100 mg daily was restarted for hypertension. Serum creatinine from early

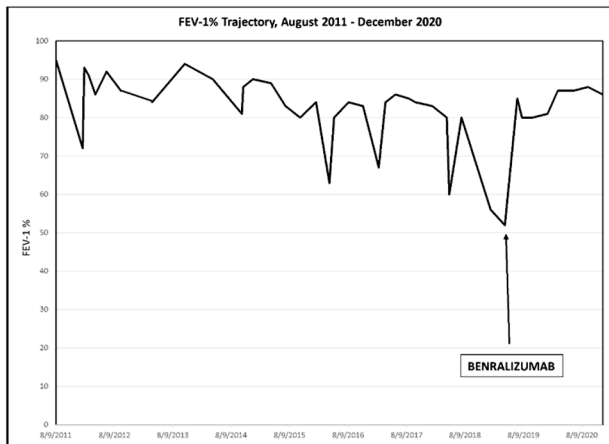


Figure 1. FEV-1% trajectory, August 2011 – December 2020.

2021 remained stable at 0.83 mg/dL. Serum albumin has been normal since April 2006 and urinalysis remained negative for dipstick proteinuria and dipstick hematuria. Urine protein to creatinine ratio was 0.43 mg/mg in early 2021 with controlled hypertension.

### Discussion

We present a case of EGPA with nephrotic syndrome diagnosed fifteen years ago, then in a 38-year-old Caucasian male. Initially, the patient had responded promptly to immunosuppression with corticosteroids and intravenous cyclophosphamide with resolution of Bell's palsy, edema and nephrotic syndrome, normalization of serum albumin, ESR had normalized and urine protein creatinine ratio had decreased from 11.6 mg/mg to 0.07 mg/mg after two months of immunosuppression. Eosinophilia responded similarly and was down to 0% after one week of immunosuppressive therapy. However, for over ten years, multiple attempts at weaning him off oral corticosteroids and mycophenolate mofetil had proved futile. In 2017-2018, despite continued administration of combination immunosuppression with oral corticosteroids and mycophenolate mofetil, together with inhalers and daily montelukast, the patient had repeatedly experienced harrowing frequent and intense asthma exacerbations, with eosinophilia sometimes ranging as high as 12%-18%. He required repeated tapered dose escalations of the prednisone to as high as 50 mg daily. As a result of these recurring asthma exacerbations, albeit without other systemic manifestations of EGPA, in April 2019, his allergy/immunology specialist started him on benralizumab, an anti-IL-5 receptor antibody, 30 mg subcutaneously every four weeks for three doses and thereafter benralizumab was administered every eight weeks. His asthma symptoms resolved quickly, eosinophil count promptly dropped to and has remained at zero, and he subsequently was weaned off mycophenolate mofetil and prednisone, 14 and 16 months, respectively, after starting benralizumab (Figures 1 and 2). Our patient would

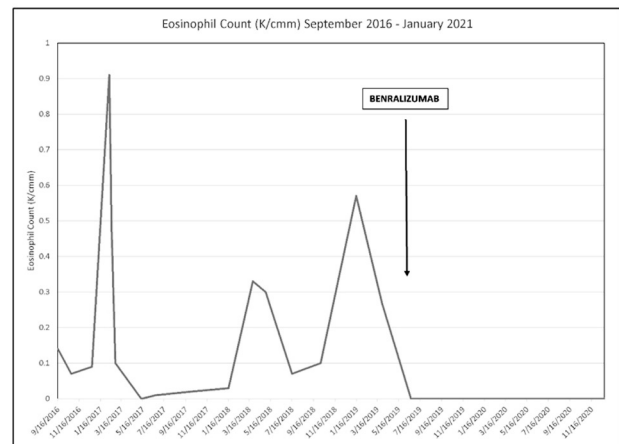


Figure 2. Trend of eosinophil count before and after the introduction of Benralizumab in April 2019

fit into the diagnostic category of asthma-dominant EGPA. Recently, Guntur et al concluded that benralizumab was well tolerated, facilitated oral corticosteroid reduction and reduced exacerbations in EGPA (9). Successful substitution monotherapy with benralizumab has only been recently and rarely reported (10). The patient described by Chica-Guzmán et al with EGPA and who was treated with benralizumab, had more features of EGPA with vasculitis and in their report, the patient had also demonstrated decreased eosinophil count (10). Our patient was different since he exhibited asthma-dominant EGPA and his eosinophil count response was dramatic, all the way down to 0% and this profound suppression of eosinophilia was sustained (Figure 2). Furthermore, our patient's features of asthma-dominant EGPA were strongly supported by the rapid response of the pulmonary function as depicted by the prompt and sustained improvement of FEV-1% with benralizumab (Figure 1). This improvement and stabilization of his FEV-1% was maintained after coming off mycophenolate mofetil and prednisone, respectively. The asthma specialist had in two previous similar cases observed unimpressive results with mepolizumab and this experience had informed his preference to administer benralizumab in this patient.

### Conclusion

We have described successful benralizumab substitution monotherapy in asthma-dominant EGPA. We therefore support calls for larger trials into the use of these new biologicals in the management of EGPA.

### Authors' contribution

MACO, BL and ML were the co-authors of this case report. MACO, BL and ML were involved in preparing the concept and design. MACO, BL and ML revisited the manuscript and critically evaluated the intellectual contents. All authors participated in preparing the final draft of the manuscript. All authors have read and approved the content of the manuscript and confirmed the accuracy or integrity of any part of the work.

**Conflicts of interest**

The authors declare that they have no competing interests.

**Ethical issues**

The wife of the patient has given us written informed consent for publication of this case. Ethical issues (including plagiarism, data fabrication and double publication) have been completely observed by the authors.

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