Benralizumab: Resolution of Eosinophilic Pulmonary Vasculitis in a Patient With EGPA

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Eosinophilic granulomatosis with polyangiitis (EGPA) is a type of small-vessel vasculitis characterized by multisystemic manifestations, including asthma and blood and tissue eosinophilia [1]. While not fully understood, pathogenesis is likely driven by the interplay between T and B cells and eosinophils [2,3]. Pulmonary involvement, which is clinically characterized by severe asthma, is a hallmark of EGPA. Currently available therapies such as corticosteroids and immune modulators are not always sufficient, and relapses are common [4]. However, the recently approved anti-interleukin (IL) 5 monoclonal antibody (mAb) mepolizumab could be an alternative treatment for EGPA affecting the lung [5,6]. Benralizumab is a fully humanized afucosylated, anti-IL-5 receptor α-chain antibody that has been approved by the United Stated Food and Drug Administration for treatment of eosinophilic asthma, and there is growing evidence of its usefulness in EGPA [7,8].

The patient was a 53-year-old man previously diagnosed with EGPA owing to the presence of asthma, marked peripheral blood eosinophilia (4.0×10^9/L, 36%), pulmonary infiltrates on a high-resolution chest tomography scan, heart failure associated with signs of vasculitis on a magnetic resonance scan, and nasal polyposis. In November 2014, he presented with a history of refractory asthma symptoms despite a daily dose of 25 mg of prednisone combined with a maximum dose of inhaled corticosteroids and long-acting $ß_2$ agonists according to step 5 of the GINA guidelines. The

Table. Clinical and Functional Data Over Time

		OCS, mg	Eos/μL	Eos, %	FEV_1, L	FEV_1, %	ACT	ACQ5	SNOT22
	Pre	25	1400	17.8	1.42	48	15	2.6	74
Mepolizumab, mo									
	+6	10	110	2.4	1.57	53	20	1.6	38
	+12	8.5	90	1.7	1.85	65	8	3.8	42
	+18	12.5	70	1.2	2.25	70	10	3.8	56
Benralizumab, mo									
	+6	8.5	0	0	2.21	71	22	1.4	31
	+12	7.5	0	0	2.73	78.6	20	1.6	19

Abbreviations: ACQ5, Asthma control Questionnaire-5; ACT, Asthma Control Test; Eos, eosinophils; FEV_1, forced expiratory volume in the first second; FVC, forced vital capacity; OCS, oral corticosteroids (mg of prednisone); SNOT22, Sinonasal Outcome Test-22.

scores on the Asthma Control Test (ACT), Asthma Control Questionnaire-5 (ACQ5), and Sinonasal Outcome Test-22 (SNOT22) were 12, 2.6, and 74, respectively. Pulmonary function tests revealed an FEV_1 of 1.42 L (48%) and FEV_1/FVC of 61.5%, with an increase of 14.1% (or 200 mL) in the reversibility test. The patient had already been treated with methotrexate and azathioprine, although both were discontinued owing to hepatotoxicity, and cyclosporine A, which was discontinued owing to inefficacy. The patient rejected therapy with cyclophosphamide. Taking into account the high serum levels of tumor necrosis factor (TNF) α, the anti-TNF-α mAb infliximab was prescribed off-label (5 mg/kg) every 8 weeks after the initial induction phase. The patient received a total of 15 doses along with 15 mg/d of prednisone but only achieved partial clinical control of his asthma (ACT, 15), with persistence of exacerbations (6 per year) and high blood eosinophilia (17.8%, 1400/μL). In May 2017, the patient started therapy with subcutaneous mepolizumab 300 mg every 4 weeks. These initially led to an improvement in the ACT score, which reached 20 after the first 3 doses, and a steep drop in blood eosinophils (0.7%, 5/μL). The dose of oral prednisone was also reduced significantly (10 mg/d). Despite a slight improvement in FEV_1 (1.85 L, 65%), after the tenth administration we observed generalized and progressive worsening of the ACT score (from 20 to 8) and daily asthma exacerbations. Chest auscultation revealed diffuse expiratory wheezing. The patient underwent a chest computed tomography scan, which showed no pleural-parenchymal abnormalities. Electrocardiogram and echocardiography findings were normal. We proceeded with bronchoscopy and bronchoalveolar lavage (BAL), which revealed normal cell values (lymphocytes 9% with a CD4/CD8 ratio of 1.6; monocytes/macrophages, 74%; neutrophils, 4%, eosinophils, 0%). Despite the lack of eosinophils in the BAL specimen and the absence of chest computed tomography findings consistent with small-vessel involvement, a transbronchial biopsy highlighted eosinophil infiltration at the capillary wall level, thus enabling a diagnosis of eosinophilic vasculitis (capillaritis) associated with moderate bronchial wall thickening and smooth muscle cell hyperplasia (Supplementary Figure 1A). The Birmingham Vasculitis Activity Score (BVAS) was 8. To demonstrate whether infiltrating eosinophils expressed IL-5Rα we proceeded with the immunohistochemical analysis using an anti-IL-5Rα polyclonal antibody (ThermoFisher, Product PA5-25159). As shown in Supplementary Figure 1B, a positive result for IL-5Rα expression was observed. In April 2019, treatment with subcutaneous benralizumab was started at 30 mg every 4 weeks for the first 2 months and then every 8 weeks as per protocol. Respiratory symptoms improved significantly after the first infusion, as shown by the ACT score, which increased from 8 to 17, and remained stable throughout the first year (mean ACT value, 20). A positive trend was also observed for the ACQ5, which decreased from 3.8 to 1.4, as did the SNOT-22 score, which was 54 before starting therapy with benralizumab, falling to 25 after only 1 dose and remaining stable throughout therapy. We also observed a moderate additional increase in FEV_1 (2.21 L, 71%) and complete negativization of the blood eosinophil count. Prednisone was therefore tapered to 7.5 mg daily, and the BVAS fell to 1. After 1 year of therapy, the patient underwent another bronchoscopy procedure with BAL, which revealed normal lymphocyte values (lymphocytes, 15%; macrophages, 85%) and absence of eosinophils. Histology of the transbronchial biopsy specimen revealed a bronchial mucosa with rarefied cellular infiltration and no eosinophils at the submucosal level. No eosinophilic vasculitis was observed (Supplementary Figure 1C). Immunohistochemistry confirmed the absence of IL-5Rα–positive cells (Supplementary Figure 1D).

The clinical data presented in this case (Table) confirm that benralizumab induces rapid and stable depletion of blood eosinophils. Since this is associated with reduced respiratory and nasal symptoms in patients with EGPA [9], corticosteroids can be tapered. Our results also suggest that the absence of eosinophils in the BAL specimen does not rule out the presence of pulmonary vasculitis. It is important to note that benralizumab led to almost complete resolution of eosinophilic vasculitis, even though we are aware that a single biopsy sample cannot rule out the presence of vasculitis in other areas.

The loss of response to mepolizumab observed in the case we report could be explained by the development of antidrug antibodies that we have not yet had the opportunity

to investigate. In addition, other cytokines able to influence eosinophil effector functions, such as IL-3, may replace IL-5 in the inflammatory process. We can also hypothesize that the eosinophils infiltrating the vascular walls may be IL-5–independent. The mode of action of benralizumab could be the reason it overcame a redundant cytokine mechanism by directly targeting eosinophils. Finally, the capacity of mepolizumab to reach these tissues may be insufficient.

To our knowledge, this is the first description of the ability of benralizumab to resolve eosinophilic infiltrates in vasculitis, even at a dose of 30 mg every 8 weeks. Although more data are required, benralizumab may represent a therapeutic opportunity for EGPA patients.

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Conflicts of Interest

Drs Vultaggio and Matucci are participating in a recently approved research project sponsored by AstraZeneca and have both received payment for advisory boards and talks from Novartis, GSK, Sanofi, Chiesi, and AstraZeneca. The remaining authors declare that they have no conflicts of interest.

References

1. Jennette JC, Falk RJ, Bacon PA, Basu N, Cid MC, Ferrario F, et al. 2012 revised international chapel hill consensus conference nomenclature of vasculitides. Arthritis Rheum. 2013;65:1-11.
2. Khoury P, Grayson PC, Klion AD. Eosinophils in vasculitis: characteristics and roles in pathogenesis. Nat Rev Rheumatol. 2014;10:474-83.
3. Wechsler ME, Akuthota P, Jayne D, Khoury P, Klion A, Langford CA, et al. EGPA Mepolizumab Study Team Mepolizumab or placebo for eosinophilic granulomatosis with polyangiitis. N Engl J Med. 2017;376(20):1921-32.
4. Faverio P, Bonaiti G, Bini F, Vaghi A, Pesci A. Mepolizumab as the first targeted treatment for eosinophilic granulomatosis with polyangiitis: a review of current evidence and potential place in therapy. Therapeut Clin Risk Manag. 2018;14:2385-96. eCollection 2018. Review.
5. Díaz Campos RM, Prudencio Ribera VC, García Moguel I, Fernández-Rodríguez C, Corral Blanco M, Jarrin Estupiñan ME, et al. Mepolizumab for the Treatment of Eosinophilic Granulomatosis With Polyangiitis: Our Experience. J Investig Allergol Clin Immunol. 2019;29(5):384-5.
6. Takenaka K, Minami T, Yoshihashi Y, Hirata S, Kimura Y, Kono H. Decrease in MPO-ANCA after administration of benralizumab in eosinophilic granulomatosis with polyangiitis. Allergol Int. 2019;68(4):539-40.
7. Kolios AGA, Lutterotti A, Kulcsar Z, Renner T, Rudiger A, Nilsson J. Benralizumab in Eosinophilic Granulomatosis with Polyangiitis complicated by Staphylococcus aureus sepsis. Clin Immunol. 2020;222:108574.
8. Dávila González I, Moreno Benítez F, Quirce S. Benralizumab: A New Approach for the Treatment of Severe Eosinophilic Asthma. J Investig Allergol Clin Immunol. 2019; 29(2):84-93.
9. Coppola A, Flores KR, De Filippis F. Rapid onset of effect of benralizumab on respiratory symptoms in a patient with eosinophilic granulomatosis with polyangiitis. Respir Med Case Rep. 2020;30:101050.

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