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 × 10⁹/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 β₂ agonists according to step 5 of the GINA guidelines. The
Birmingham Vasculitis Activity Score (BVAS) was 8. To rule out the presence of pulmonary vasculitis. It is important to note that benralizumab led to almost complete resolution of 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 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 FEV1 (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

### Table. Clinical and Functional Data Over Time

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<th>Eos/µL</th>
<th>Eos, %</th>
<th>FEV1, L</th>
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Abbreviations: ACQ5, Asthma control Questionnaire-5; ACT, Asthma Control Test; Eos, eosinophils; FEV1, forced expiratory volume in the first second; FVC, forced vital capacity; OCS, oral corticosteroids (mg of prednisone); SNOT22, Sinonasal Outcome Test-22.
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