Benralizumab: Blowing Out Eosinophilic Pulmonary Vasculitis in A EGPA Patient

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Key words: Asthma. Eosinophilic vasculitis. Bronchial alveolar lavage. Benralizumab. EGPA.

Palabras clave: Asma. Vasculitis eosinofílica. Lavadobroncoalveolar. Benralizumab. GEP.

Eosinophilic granulomatosis with polyangiitis (EGPA) is a small vessel vasculitis characterized by multi-systemic manifestations, including asthma, blood and tissue eosinophilia [1]. The pathogenesis, although still not fully understood, is likely driven by the interplay between T and B cells and eosinophils [2,3]. Pulmonary involvement clinically characterized by severe asthma, is a hallmark of EGPA. Current available therapies such as corticosteroids and immune modulators are not always sufficient and relapses are common [4], but recently the anti-interleukin (IL)-5 monoclonal antibody (mAb) mepolizumab has been approved as alternative treatment for pulmonary localization of EGPA [5,6]. Moreover, benralizumab, a fully humanized afucosilated anti-IL-5receptor α-chain antibody, is FDA approved for the therapy of eosinophilic asthma and there is growing evidence of its use in EGPA [7,8].

In November 2014, a 53 year old male patient previously diagnosed with EGPA for the presence of asthma, marked peripheral blood eosinophilia ($4.0x10^9$/L, 36%) pulmonary infiltrates at high resolution chest tomography scan, heart failure associated with MRI-documented vasculitis signs, and nasal polyposis presented with a history of refractory asthma symptoms despite a daily dose of 25 mg of prednisone in addition to a maximal dose of inhaled steroids and long-acting beta2 agonists (LABA) according to GINA step V of guidelines. The asthma control test (ACT), asthma control questionnaire-5 (ACQ5) and sinus nasal outcome test-22 (SNOT22) were 12, 2.6, and 74, respectively. Pulmonary function tests displayed a FEV1 of 1.42L (48%) and a FEV1/FVC of 61.5% with an increase of 14.1% (or 200ml) at the reversibility test. The patient had already been treated with methotrexate and azathioprine both discontinued due to hepatotoxicity, and cyclosporine A, also discontinued due to inefficacy.

doi: 10.18176/jiaci.0689

Cyclophosphamide was not administered due to patient refusal. Taking into account the high serum levels of tumor necrosis factor (TNF)-α, anti-TNF-α mAb infliximab was used in a off label strategy (dose of 5 mg/kg) every eight weeks after the initial induction phase. He underwent a total of 15 doses along with 15 mg/day of prednisone, but was able to only reach partial clinical asthma control (ACT 15), with persistence of exacerbations (6/year) and high blood eosinophilia (17.8%, 1.400 cells/mmc). In May 2017 the patient was started on mepolizumab 300mg subcutaneous injections every four weeks which initially allowed for ACT improvement, reaching the ACT value of 20 after the first three doses, and a steep drop in blood eosinophils (0.7%, 5 cells/mmc). A significant reduction of oral prednisone dose was also observed (10 mg/day). Despite a slight improvement of FEV1 (1.85L, 65%), after the 10th administration we observed an overall and progressive worsening of ACT (from 20 to 8) and daily asthma exacerbations. On physical examination, chest auscultation revealed diffuse expiratory wheezing. The patient was administered a chest CT which showed no pleuro-parenchimal alterations. Electrocardiogram and echocardiography were normal. We proceeded with bronchoscopy with bronchial alveolar lavage (BAL) which highlighted a normal cellular population (lymphocytes 9% with CD4/CD8 ratio of 1.6; monocytes/macrophages 74%; neutrophils 4%, eosinophils 0%). Despite the lack of eosinophils in BAL and absence of chest CT findings consistent with small vessel involvement, a trans-bronchial biopsy highlighted eosinophil infiltration at the capillary wall level allowing for the diagnosis of eosinophilic vasculitis (capillaritis) associated with a moderate bronchial wall thickening and smooth muscle cell hyperplasia (see supplementary Figure 1A). Brimingham Vasculitis Activity Score (BVAS) was 8. To demonstrate whether infiltrating eosinophils expressed IL-5Rα we proceeded with the immune-histochemical (IHC) analysis by using an anti-IL-5Rα polyclonal antibody (ThermoFisher Product PA5-25159-Massachussets-USA). As shown in supplementary Figure 1B, a positive result of IL-5Rα expression was observed. In April 2019 treatment with

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benralizumab was started at the dose of 30mg subcutaneous injections at 4 week intervals for the first two months and then every 8 weeks as per protocol. Respiratory symptoms significantly improved after the first infusion, as shown by ACT score which increased from 8 to 17, and were maintained stable throughout the first year (ACT mean value: 20). The ACQ5 also showed a positive trend, decreasing from a score of 3.8 to 1.4, as well as the SNOT-22 which was 54 before starting therapy with benralizumab and decreased to 25 after just one dose, and remained stable throughout therapy. We also observed a moderate additional increase of FEV1 (2.21L, 71%) and complete negativization of the blood eosinophil count. This allowed for steroid tapering to prednisone 7.5mg daily, and reaching BVAS 1. After one year of therapy the patient underwent another bronchoscopy procedure with BAL which showed normal patterns of lymphocytic numbers (lymphocytes 15%, macrophages 85%) and absence of eosinophils. The trans-bronchial biopsy's histological examination showed a bronchial mucosa with rarefied cellular infiltration and no eosinophils at the submucosal level. No eosinophilic vasculitis was observed (supplementary Figure 1C). The IHC confirmed the absence of IL-5Rα-positive cells (supplementary Figure 1D).

The clinical data presented in this case, which has been summarized in Table 1, confirms that benralizumab is able to induce a rapid and stable depletion of blood eosinophils, associated with a reduction of respiratory and nasal symptoms in patients with EGPA [9], thus allowing for a steroid sparing effect. Our case suggests that the absence of eosinophils in BAL does not rule out the presence of pulmonary vasculitis. It's important to note that benralizumab was able to obtain an 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 our patient could be explained by the development of anti-drug antibodies, that however 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. In fact, we can also hypothesize that the

doi: 10.18176/jiaci.0689

eosinophils infiltrating the vascular walls may be IL-5 independent. Benralizumab's mode of action could be the reason for overcoming a redundant cytokine mechanism by directly targeting eosinophils. Finally, the capacity of mepolizumab to reach these tissue sites may be insufficient.

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

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Table 1: Clinical and functional data over time

	OCS (mg)	**Eos** (cell/mm^3)	**Eos** (%)	**FEV1** (L)	**FEV1** (%)	**ACT**	**ACQ5**	**SNOT22**
Pre	25	1400	17.8	1.42	48	15	2.6	74
Mepolizumab								
months								
+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								
months								
+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

Asthma control Questionnaire-5 (ACQ5); Asthma Control Test (ACT); Eosinophils (Eos); Forces expiratory volume in the 1st second (FEV1); Forces vital capacity (FVC); SinuNasal Outcome Test-22 (SNOT22); Oral corticosteroids (OCS, mg of prednisone.

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