

Journal Pre-proof

Eosinophilic Granulomatosis with Polyangiitis Successfully Treated with Benralizumab.

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PII: S1081-1206(20)30321-5

DOI: <https://doi.org/10.1016/j.anai.2020.05.002>

Reference: ANAI 3239

To appear in: *Annals of Allergy, Asthma and Immunology*

Received Date: 19 March 2020

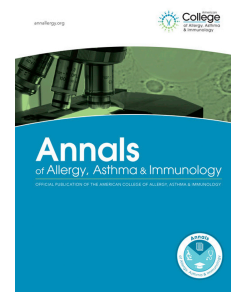
Revised Date: 30 April 2020

Accepted Date: 3 May 2020

Please cite this article as: Chica-Guzmán MV, Morillo-Guerrero R, Carrón-Herrero A, González-de-Olano D, Almonacid-Sánchez C, Eosinophilic Granulomatosis with Polyangiitis Successfully Treated with Benralizumab., *Annals of Allergy, Asthma and Immunology* (2020), doi: <https://doi.org/10.1016/j.anai.2020.05.002>.

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1 Title page

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5 **Eosinophilic Granulomatosis with Polyangiitis Successfully Treated with**
6 **Benralizumab.**

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27 **Fundings:** No funding has been required for the present study.

28

29 Word count: 748

30 Number or tables or figures: 1

31

32 The authors certify that any of them have any conflict of interests.

33

34 **Key words**

35 Anti-IL-5 therapies; Asthma; Benralizumab; Eosinophilic granulomatosis with
36 polyangiitis; Mepolizumab; Monoclonal antibodies; Omalizumab.

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38 **Contribution of each author**

	Conception	Data generation	Analysis	Revision	Approval
Vanessa Chica-Guzman	X	X	X	X	X
Raquel Morillo-Guerrero		X	X	X	X

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David González-de-Olano	X	X	X	X	X
C. Almonacid-Sánchez	X	X	X	X	X

Eosinophilic granulomatosis with polyangiitis (EGPA) is a rare but potentially life-threatening antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis which affects, to varying degrees, the lungs, paranasal sinuses, heart, kidneys, skin and peripheral nervous system. It is strongly associated with asthma. Peripheral eosinophilia is a defining feature of EGPA and eosinophilic inflammation is often observed in biopsies of affected tissues. The pathogenesis of EGPA is not completely clear; the disease is probably the result of complex interactions in which genetic and environmental factors lead to an inflammatory response whose main actors are eosinophils and T and B lymphocytes.¹ The activated Th-2 phenotype triggers the release of key cytokines for the activation, maturation and survival of eosinophils, such as IL-4, IL-5 and IL-13.² In particular, IL-5 is highly increased in active EGPA and its inhibition may represent a potential therapeutic target.^{2,3} High eosinophil levels are an integral part of the diagnosis of EGPA, and have a cytotoxic and pro-coagulant effect that may cause the development of cardiovascular and cerebrovascular complications in patients with any type of hypereosinophilic syndrome, including EGPA. Acute and chronic management focuses on the control of inflammation with systemic corticosteroids and other immunosuppressants, all of which carry a significant burden of adverse effects. The development of monoclonal antibody therapies against interleukin-5 (IL-5), the major driver of eosinophilic inflammation, has therefore garnered significant interest among clinicians treating EGPA.

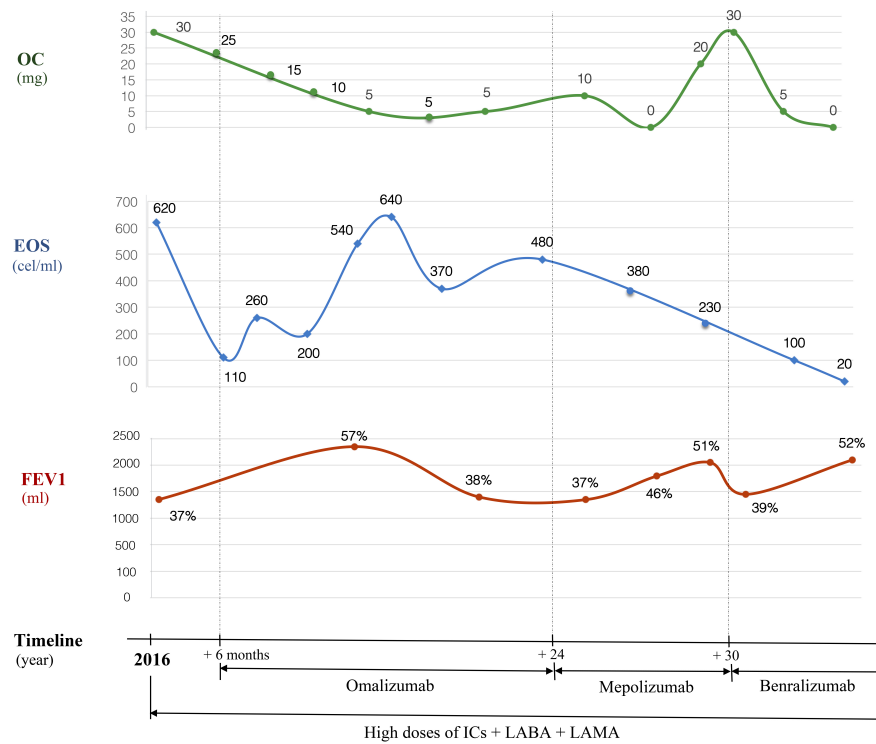
We report one case of a 53-year-old male with a history of chronic rhinosinusitis with nasal polyposis, bronchial asthma, eosinophilia (620 cells / mm³) and hypesthesia affecting mainly to the left superficial peroneal nerve and tibialis anterior muscle. A biopsy presented an increased number of eosinophils, and the electromyogram showed

asymmetric motor-sensory axonal polyneuropathy, consistent with multiple multineuritis. He was finally diagnosed with EGPA in 2002 and began treatment with high doses of long-acting beta-agonists (LABA), long-acting muscarinic-antagonist (LAMA) and oral corticosteroids (OCs) with daily doses ranging from 60 mg to 10 mg for 14 years. In an attempt to lower the dose of OCs, treatment with cyclophosphamide (100 mg) was attempted, but this treatment was suspended after 12 months since no improvement was observed. In 2016, he started on omalizumab (600 mg every 4 weeks) for 2 years with partial response, reducing doses of OC to 5 mg/day, but with worsening of pulmonary function, so the treatment was changed to mepolizumab 100 mg monthly with good response at the beginning of the treatment. Corticosteroids were initially suspended, but after 6 months the patient required high doses of OCs (30 mg daily) due to a decrease in forced expiratory volume in 1 second (FEV1) values. For that reason, treatment was changed to benralizumab (30 mg/monthly during the first 3 months and afterwards to 30 mg every 2 months). The patient presented clinical improvement, a decrease in peripheral eosinophils and complete suspension of OCs after 6 months of treatment was achieved (see Figure 1).

Mepolizumab is an anti-interleukin-5 (IL-5) agent indicated for the treatment of severe eosinophilic asthma.⁴ Its use has been explored with good results in other diseases that share some pathogenic mechanisms with eosinophilic asthma, including EGPA,⁵ although an increased dose of 300 mg per month have been proposed.⁶ Benralizumab has the advantage over other anti-IL-5 therapies to target the IL-5 receptor α (IL-5R α) on eosinophils. It has been reported to reduce the exacerbation rate in patients with blood eosinophil counts of at least 300 cells/ μ l, to improve FEV1,^{7,8} and to decrease the need of OCs or even withdraw them.⁹ Currently, there is a clinical trial Phase III study

(NCT03010436) about the efficacy and safety of benralizumab in the treatment of EGPA, and it also has been reported one case of good response after 3 months of treatment.¹⁰

We present a case of EGPA with partial improvement after the administration of omalizumab and mepolizumab. The latter was used at the recommended dose for asthma (100 mg), since the use of higher doses was not authorized in our center at that time. Finally, treatment with benralizumab led to a sustained clinical improvement along with a withdrawal of OCs. The use of anti-IL5 and IL-5 receptor α may be considered as an option for the treatment of EGPA in those patients who do not respond to the usual treatments, especially those requiring high and prolonged doses of oral corticosteroids. The existence of new therapeutic tools focused on specific targets may be useful in the management of complex, life-threatening pathologies that sometimes do not respond to conventional treatment which usually carry significant adverse effects.



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Figure 1. Evolution of patient with eosinophilic granulomatosis with polyangiitis after administration of different treatments.

IC, inhaled corticosteroids; EOS, eosinophils; FEV1, forced expiratory volume in 1 second; LABA, long-acting beta-agonists; LAMA, long-acting muscarinic-antagonist; OC, oral corticosteroids.