A case of protracted eosinopenia after a single subcutaneous dose of benralizumab

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Background

Interleukin-5 (IL-5) is a key cytokine in eosinophils differentiation, proliferation, activation, and trafficking and it is closely associated with asthma symptoms and exacerbations [1]. Several anti-IL-5 monoclonal antibodies (mAbs) have been developed for the treatment of severe eosinophilic asthma. Inhibition of IL-5 significantly reduces blood and sputum eosinophils in asthmatic patients. However, tissue eosinophils are only partially removed, presumably due to other cytokines that can promote eosinophil survival [2]. Benralizumab is a humanized, afucosylated Immunoglobulin G1k (IgG1k) monoclonal antibody, directed against the α subunit of the IL-5 receptor. It inhibits IL-5 from binding to its specific receptor, thus, inhibiting the proliferation of IL-5-dependent cell lines. Furthermore, it directly targets and depletes eosinophils and other IL-5R+ cells by inducing antibody-dependent cell-mediated cytotoxicity (ADCC), differentiating it from the other IL-5 ligand targeted therapies [3].

A 30 mg dose administered subcutaneously once every 4 weeks for the first 3 doses, and once every 8 weeks thereafter, is recommended. However, studies have reported persistent peripheral blood (PB) eosinophil suppression up to 12 weeks after an isolated intravenous (iv) administration of benralizumab at doses ranging from 0.3 to 3 mg/kg [4]. Real-life data regarding the effect of a single dose of subcutaneous (sc) benralizumab on patient’s PB eosinophils and symptoms is, however, still lacking.

Case representation

We report a 61-year-old woman with severe eosinophilic asthma and bilateral chronic rhinosinusitis without nasal polyps or history of sinus surgery. She had blood eosinophilia (560 cells/μL, evaluated without the use of systemic corticosteroids [sCort]) and normal total IgE (57 kU/L). GINA step-5 treatment was implemented with additional aminophylline 225 mg twice daily.

Despite the patient’s good compliance, she had frequent asthma exacerbations requiring emergency department visits, multiple sCort courses, and hospitalizations. Maintenance therapy with prednisolone 5 mg/daily was attempted with only a slight improvement. Despite this, and although she did not require hospitalizations, she nonetheless presented with a total of six asthma exacerbations with transient corticosteroid dose increase in the 12 months before the new treatment was proposed. Considering the patient’s characteristics, most convenient posology, and lower economic burden compared with other possible mAbs, 30 mg of sc benralizumab was started in October 2020. The second dose was skipped because the patient was infected with SARS-CoV-2, and performed in December 2020. The interval between the two administrations was approximately 3 months (82 days). Amid both applications, against our recommendation, the patient discontinued sCort and aminophylline due
to self-notion of clinical improvement. Immediately before the second administration, PB eosinophil depletion (0 cells/μL) and also improvement of clinical and quality of life were observed. Clinical and functional follow-up measures are presented in Table 1. No side effects were reported.

Surprisingly, there was no significant improvement regarding her nasal symptoms at that time, but it was attributed to the recent severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, since she afterwards had a total CARAT score of 26 (8+18) and a sino-nasal outcome test (SNOT-22) of 8. However, a distinct efficiency of benralizumab on the upper and the lower airway cannot be ruled out in this situation.

The patient is presently under benralizumab 30 mg sc every 8 weeks, fluticasone furoate/umeclidinium/vilanterol (92/55/22 mcg) Ellipta® (Glaxo Wellcome Production, Évreux, France), without any need for reliever therapy, sCort, or aminophylline.

Although sustained eosinopenia after an isolated iv administration of benralizumab has been reported [4], to our knowledge this is the first case related to single subcutaneous administration in an asthmatic patient with previous eosinophilia. In addition, clinical improvement was maintained despite the interval between administration, with an improvement in peak expiratory flow regardless of stepping down the maintenance therapy. A similar phenomenon has been reported by Martínez-Rivera et al., after an isolated administration of benralizumab [5].

### Conclusion

This report raises the possibility and success of patient-tailored scheduling of benralizumab administration as an alternative to the current regimen. Prospective studies and long-term follow-up are still required to confirm this hypothesis.

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### Author Contribution

The manuscript has been read and approved by all the authors. J. Miranda, J. Plácido, and L. Amaral designed and wrote the manuscript. The manuscript has not been published previously in print/electronic format (except in the form of an abstract) or in another language and is not under consideration by another publication or electronic media.

### Conflict of interest

J. Miranda, J.L. Plácido and L. Amaral declare that they have no competing interests. The authors have no relevant financial or non-financial interests to disclose.

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### Table 1 Follow-up measures results

|                     | September 2020<sup>a</sup> (plethysmography) | December 2020<sup>b</sup> | February 2021<sup>c</sup> (spirometry) |
|---------------------|-----------------------------------------------|--------------------------|------------------------------------------|
| CARAT               | 10 (4 + 6)                                    | 20 (4 + 16)              | 26 (8 + 18)                              |
| ACT                 | 12                                            | 22                       | 24                                       |
| E05D                | 21 222—65%                                    | 11 111—85%              | 11 111—90%                              |
| SNOT                | –                                             | –                        | 8                                        |
| FVC (L)             | 2.75                                          | –                        | 2.41                                     |
| FEV₁ (L)            | 1.72                                          | –                        | 1.63                                     |
| PEF (L/s)           | 4.24                                          | –                        | 4.33                                     |
| PB eosinophils (cells/μL) | –                  | 0.0                      | 0.0                                      |

<sup>a</sup>Under prednisolone 5 mg/daily, before the first benralizumab administration

<sup>b</sup>After the first and before the second benralizumab administration

<sup>c</sup>CARAT control of allergic rhinitis and asthma test, ACT asthma control test, E05D EuroDol-SD, SNOT-22 sino-nasal outcome test, PFT pulmonary function test, FVC forced vital capacity, FEV₁ forced expiratory volume in 1 s, PEF peak expiratory flow, PB peripheral blood