
Severe Eosinophilic Allergic Asthma Responsive to Mepolizumab After Failure of 2 Consecutive Biologics

Sánchez-Jareño M¹, Barranco P^{1,2}, Romero D³, Domínguez-Ortega J¹, Quirce S^{1,2}

¹Department of Allergy, Hospital La Paz Institute for Health Research (IdiPAZ), Madrid, Spain

²CIBER de Enfermedades Respiratorias, Ciberes, Madrid, Spain

³Department of Pneumology, Hospital La Paz, Madrid, Spain

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In recent years, biological treatments have become a new therapeutic option for patients with severe asthma whose disease is not controlled with standard treatments [1]. These new therapeutic agents have been shown to be both selective and effective, as they act by blocking specific inflammatory pathways [2]. However, it is becoming increasingly difficult to select a biologic from which the patient may benefit, since there are no specific, validated biomarkers that can predict a good response. The overlap of various inflammatory pathways in asthma phenotypes could explain the lack of success of targeted therapies in certain cases [3]. Severe allergic eosinophilic asthma is an example of such a challenging scenario. In this common asthma phenotype, the underlying mechanisms responsible for asthma symptoms may be linked to heterogeneous type 2 inflammatory pathways, making patients eligible for treatment with anti-IgE, anti-IL-13, and anti-IL-5 [4]. As there are no definite recommendations to prescribe one biologic over another, treatment must be switched if asthma control is not achieved [5].

A 51-year-old man was referred to the Asthma Unit of Hospital La Paz, Madrid, Spain in 2014 with uncontrolled severe asthma. Over the previous 10 years, he had worked as a laboratory technician. His clinical history was remarkable for the following: ex-smoker for 14 years (7 pack-years), severe allergic asthma diagnosed in 2004, several nasal polyp surgeries, and aspirin-exacerbated respiratory disease. He had no suggestive history of occupational respiratory disease. Even though he was treated with maintenance doses of 5 to 10 mg of prednisone, high doses of inhaled corticosteroid/long-acting β -agonist (ICS/LABA), and leukotriene inhibitors, he had experienced 4-5 asthma exacerbations per year during the previous 4 years. Omalizumab 300 mg monthly was initiated as add-on therapy. Despite receiving omalizumab for 1 year and prednisone 5 mg daily, he continued to experience severe asthma attacks with frequent visits to the emergency department. Omalizumab was then stopped, and he was

Table. Patient's Progress

Date	Lung Function	FeNO, ppb	Eosinophils/ mm ³	ACT, Points	Clinical Outcomes	Treatment
March 2014	FVC 4.59 L (91%) FEV ₁ 2.49 L (61.4%) FEV ₁ /FVC 54.38% Positive bronchodilation test (FEV ₁ +22%, FEV ₁ /FVC 70%)	192	1120	11	First visit to ACD Unit Inclusion in LAVOLTA clinical trial	Salmeterol/ fluticasone 22/250: 2 puffs bid Montelukast 10 mg/ 24 h Tiotropium: 18 µg/24 h Prednisone 5 mg/24 h
March 2015	FVC 5.04 L (93.3%) FEV ₁ 4.06 L (65.9%) FEV ₁ /FVC 56.94%	98	1400	9	Six hospital admissions. End of placebo period. Initiation of lebrikizumab period.	Salmeterol/ fluticasone 22/250: 2 puffs bid Montelukast 10 mg/ 24 h Tiotropium: 18 µg/24 h Prednisone 5-10 mg/24 h
August 2016	FVC 4.71 L (95%) FEV ₁ 2.31 L (58%) FEV ₁ /FVC 49%	96	2500	10	Five hospital admissions. End of LAVOLTA clinical trial.	Prednisone 5-30 mg/24 h Formoterol/fluticasone 320/9 µg 2 puffs bid Montelukast 10 mg/24 h Tiotropium 18 µg once daily
November 2017	FVC 5.16 L (104%) FEV ₁ 2.37 L (59%) FEV ₁ /FVC 45%.	95	1400	8	Four hospital admissions. One nasal polyp surgery	Prednisone 10-30 mg/24 h Formoterol/fluticasone 320/9 µg 2 puffs bid Montelukast 10 mg/24 h Tiotropium 18 µg once daily
September 2018	FVC 4.96 L (100%) FEV ₁ 2.71 L (69%) FEV ₁ /FVC of 69%	98	50	19	No more asthma attacks. No further need for oral corticosteroids.	Vilanterol/ fluticasone furoate 184/22 once daily Montelukast 10 mg/24 h Tiotropium 18 µg once daily Mepolizumab 100 mg/4 wk

Abbreviation: ACT, Asthma Control Test.

referred to our unit. At his first visit, a specific diagnostic protocol for uncontrolled severe asthma was applied in compliance with clinical management guidelines. Pulmonary function tests demonstrated an FVC of 4.59 L (91%), FEV₁ of 2.49 L (61.4%), and severe airflow obstruction (FEV₁/FVC 54.38%). The bronchodilation test was positive after only 15 mg of prednisone daily for 2 weeks (increase in FEV₁ of 22% and in the FEV₁/FVC ratio of 70%). Fractional exhaled nitric oxide (FeNO) was 192 ppb. The Asthma Control Test (ACT) score was 11. The allergy work-up revealed positive skin prick test results to grass pollen, *Cupressus arizonica* and *Lepidoglyphus destructor*. Total serum IgE levels were 91.9 kU/L. Specific IgE antibodies (ImmunoCAP, Thermo Fisher) to grass pollen and *L destructor* were negative, although they were slightly positive to *C arizonica* pollen (1.48 kU_A/L), suggesting possible concordance with asthma attacks during winter months. A complete blood count showed peripheral blood eosinophilia (500/mm³). During asthma attacks, blood eosinophilia increased to a maximum of 1400/mm³. An immunology work-up including IgG, IgA, IgM, antineutrophil cytoplasmic antibodies, antinuclear

antibodies, and rheumatoid factor revealed no abnormalities. Microbiological and serological tests for viruses and molds were negative. A computed tomography scan of the chest and paranasal sinuses showed bronchiectasis with atelectasis in the middle lobe, and grade III nasal polyps. Other comorbidities such as gastroesophageal reflux disease or vocal cord dysfunction were ruled out. Therefore, the patient was diagnosed with severe eosinophilic allergic asthma that remained uncontrolled with standard treatments. Owing to the lack of response to this treatment and omalizumab, we proposed initiating treatment with lebrikizumab, an anti-IL-13 biologic. After giving his written informed consent, the patient was enrolled in a phase III clinical trial (LAVOLTA GB28689) [6]. He received placebo during the first year and lebrikizumab during the second. His symptoms worsened progressively throughout the 2-year clinical trial period, with 5-6 asthma exacerbations per year and 1 hospitalization. A new clinical evaluation in our unit revealed a decrease in lung function and blood eosinophilia (>2500/mm³). A stool test yielded a positive result for *Blastocystis* species. Although this infection resolved after treatment with metronidazole, blood

eosinophilia levels remained elevated (2000/mm³). Finally, the clinical trial was discontinued, and the patient returned to his regular therapy with oral corticosteroids only (prednisone 5 mg/24 h), high-dose ICS/LABA (320/9 µg 2 puffs bid), montelukast (10 mg), and tiotropium (18 µg once daily). A year later, he underwent surgery for grade III nasal polyps and had uncontrolled asthma (FVC, 5.16 L [104%]; FEV₁, 2.37 L [59%]; and FEV₁/FVC, 45%). We decided to shift treatment to a new biologic based on the patient's clinical history, asthma phenotype, and potential adverse effects of continuous high-dose corticosteroids. The patient agreed, and anti-IL-5 therapy was administered with subcutaneous mepolizumab (100 mg every 4 weeks). After 8 months with mepolizumab, lung function improved progressively with an FEV₁/FVC of 69% and an ACT score of 19. His respiratory symptoms improved markedly, and no asthma attacks occurred despite withdrawal of oral corticosteroids. His nasal polyps remained in grade I, with no need for topical medication. He did not present any adverse reactions, despite being treated with 3 different biologic therapies. Nevertheless, a longer follow-up period would be desirable.

It is important to identify the pathway involved in specific asthma phenotypes in order to tailor treatment with biological antibodies [7]. Although these agents have helped to increase our knowledge of the pathogenesis of asthma, in many instances it remains unclear which is the best approach for patients with different clinical traits and phenotypes, some of which, such as eosinophilic and allergic asthma, can overlap [8]. In this sense, recent post hoc analyses reported that mepolizumab was safe and effective for patients of this type who had previously received omalizumab [7,9,10]. In the case we report, the patient was sequentially treated with 3 biological therapies that target different selective molecules; however, only mepolizumab improved his asthma symptoms. Although several biologics have been approved for uncontrolled severe asthma, no specific biomarkers have been developed to predict a good response to these therapies. This is particularly cumbersome in patients who might qualify for omalizumab and anti-IL-5 therapies [7-10]. Further studies are needed to improve our understanding of the mechanisms involved in the different features of asthma and to optimize the selection of biologics.

We report the first case of severe uncontrolled allergic eosinophilic asthma with failure of 2 biological therapies (anti-IgE and anti-IL-13) and marked improvement with anti-IL-5.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Marta Sánchez-Jareño

Department of Allergy

Hospital La Paz

Paseo de la Castellana 261

28046 Madrid, Spain.

E-mail: martasanchezjare@gmail.com