

Effectiveness of benralizumab in severe eosinophilic asthma under routine clinical practice

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Benralizumab is a humanized IgG1 κ , afucosylated, monoclonal antibody that binds to IL-5 receptor α on the surface of human eosinophils and basophils. It induces a rapid and complete depletion of blood eosinophils, and this effect persists for at least 2 to 3 months in subjects under this treatment [1,2].

Clinical trials have shown the efficacy and safety of Benralizumab in patients with severe eosinophilic asthma by reducing annual exacerbations and improving symptoms and lung function [3,4]. Real-life studies are useful to check the effect of a treatment in routine clinical practice, and several studies have been published showing effectiveness of benralizumab [5,6]. Benralizumab is indicated in patients suffering from severe uncontrolled eosinophilic asthma [7,8].

This is a multicenter study of RE-ASGRAMUR performed in eight hospitals of the Region of Murcia (Spain) under conditions of routine clinical practice. The study was approved by the Ethics Committee.

We present a series of 84 patients diagnosed with Severe Eosinophilic Asthma after completing at least 1 year of treatment with Benralizumab, with a mean duration of treatment of 18.8 months. We analysed clinical characteristics, eosinophilia, total IgE, drug tolerance and effectiveness (decreased exacerbations, Asthma Control Test [ACT], Asthma Quality of Life Questionnaire [AQLQ], lung function [FEV1]), and use of oral corticosteroids. We used the Wilcoxon signed rank test for the statistical analysis; the

results are reported as median (IQR). Methods are described in Appendix 2 in Supplementary material.

The mean age of our patients was 59.5 years and 49 were women (58.3%). The average BMI was 29.5. Sixteen patients (20.2%) began with asthma before 18 years of age and 63 (79.8%) after this age, and the mean duration of the disease was 23,5 years in the group with nasal polyps and 22 years in the group without polyps. 43 (51.2%) had never smoked, 38 (45.2%) were ex-smokers, and 3 patients continued to smoke.

Thirty-two patients (38.1%) were atopic, 37 (44%) had chronic rhinosinusitis, and 32 (38%) had nasal polyposis. Thirty-nine patients (46%) were cortico-dependent and the mean daily dose of prednisone was 16.5 mg. The mean eosinophil count was 682, IgE 268.4, and FeNO 51.9 ppb.

The mean number of exacerbations in our patients was 4.5 and 43 (51%) had to attend the emergency department at least once in the previous year. The mean ACT was 12.5 and the mean AQLQ was 3. Regarding lung function, the mean FEV1 was 1840 ml (67.5%).

Finally, 32 (38%) patients were previously in treatment with omalizumab and 16 (19%) with mepolizumab, being suspended due to lack of response.

The baseline characteristics of our patients can be seen in the Supplementary Table 1.

The results are shown in Table 1. We found a very significant reduction in the number of exacerbations in our patients, from a median of 3 before benralizumab treatment to 0 after treatment; this decrease was similar in patients with and without nasal polyposis. It is noteworthy that 70 % of our patients had 0 exacerbations along the year of treatment vs 8% before treatment, confirming the results of other studies with Benralizumab [9]. We

could see this significant decrease of exacerbations in all the groups of patients according to the baseline level of eosinophils (Supplementary Table 2).

Regarding oral prednisone intake in cortico-dependent patients, the median decreased from 10 mg before treatment to 0 after treatment, both in the total group and in the subgroups with and without polyposis. 82% of the patients did not take oral corticosteroids after the treatment. We found this decrease in corticosteroid intake in all groups of patients regarding eosinophils, although it was up to a dose of 0 mg per day in those with more than 300 eosinophils, also confirming this effect of the drug [10].

Attending asthma control, measured by the ACT questionnaire, we have seen a relevant increase in the total group from 13 to 22 with the drug, well above the minimum important difference. This increase was greater in the polyposis subgroup.

Regarding quality of life, we have seen a significant increase in the AQLQ questionnaire, of 2.21 points, also well above the minimum important difference, as it has been seen in other studies [11]. This increase has also been greater in the subgroup with polyposis.

FeNO decreased in the total group from 38 before treatment to 29, at the expense of the group of patients without nasal polyposis, seeing a small increase in FeNO in the other group. The median of eosinophils was 615 (410-865) before treatment and 0 (0-0) after it ($p < 0.00001$) in the polyposis group, and 600 (330-900) before treatment and 0 (0-0) after it ($p < 0.00001$) in the group without polyps.

Attending lung function, we have found an increase in FEV1 from 1740 ml (69%) to 1985 ml (81.5%). This increase was greater in the group with polyposis (385 ml) than in the group without it (165 ml), confirming this comorbidity as a potential indicator of enhanced response [12]. The median basal FVC% was 85% and increased to 95,5% after the treatment; this increase was also higher in the group with polyps (12.5%) than in the

group without polyps (7%). 51 patients had a FEV1/FVC ratio under the LLN before treatment, and this situation was normalized in 17 of them after treatment.

Five patients abandoned the treatment because of side effects: one due to local pain, asthenia and refusal of treatment, another one due to influenza-like syndrome, another one due to headache, another one due to arthralgia, and another one due to bronchospasm plus headache.

Only three patients gave up the treatment due to lack of response (persistence of exacerbations, with hospital admittances in two of them): 3 women, 2 with obesity, with eosinophils: 300, 890 and 2300 cells. Two were atopic and none had nasal polyps. One was previously in treatment with omalizumab, and one with omalizumab and mepolizumab.

In conclusion, we found benralizumab to be a well-tolerated and effective treatment for patients with severe eosinophilic asthma even in patients below 300 eosinophils, decreasing both the number of exacerbations and the intake of oral corticosteroids. This treatment improved disease control, quality of life and lung function values in our patients, to a greater extent in those with nasal polyposis.

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Conflicts of interest

Juan Carlos Miralles López has received consultancy fees from Chiesi and speaker fees from Novartis, GSK, Astra Zeneca, Sanofi and Chiesi. Rubén Espinosa Andújar has received speaker fees from Novartis, GSK, Astra-Zeneca, Sanofi, and Chiesi. Francisco Javier Bravo Gutiérrez has received speaker fees from Novartis, Ferrer, GSK, Astra-Zeneca, Sanofi, and Chiesi. Manuel Castilla Martínez has received consultancy fees from GSK and Astra Zeneca and speaker fees from Novartis, GSK, Astra-Zeneca, Sanofi, and Chiesi. Isabel María Flores Martín has received speaker fees from Novartis, GSK and Sanofi. María Loreto Alemany Francés has received speaker fees from Novartis, GSK, Astra-Zeneca and Chiesi. Manuel José Pajarón Fernández has received speaker fees from GSK. José Valverde Molina has received consultancy fees from Astra Zeneca, speaker fees from Novartis, GSK, Astra Zeneca, Sanofi, Teva, Orion Pharma, and fees for advisory board from GSK and Novartis. Ana Mora González and Virginia Pérez Fernández have no conflicts of interest.

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Table I. Results

	TOTAL N = 84			Nasal Polyps N = 32			No Nasal Polyps N = 52		
	Baseline	After treatment	p	Baseline	After treatment	p	Baseline	After treatment	p
Exacerbations	3 (2-5)	0 (0-1)	< 0.00001	3 (2-5)	0 (0-0)	< 0.00001	4 (2-6.5)	0 (0-1)	< 0.00001
Oral prednisone	10 (5-20)	0 (0-5)	< 0.00001	10 (5-20)	0 (0-2.5)	0.0013	10 (5.5-20)	0 (0-5)	< 0.00001
ED visits	1 (0-3)	0 (0-0)	< 0.00001						
ACT	13 (8-16)	22 (18.5-24)	< 0.00001	11 (9-14)	23 (19.5-24)	< 0.00001	13 (8-16)	21 (16-23)	< 0.00001
AQLQ	2,86 (2.27-3.7)	5.07 (4.07-5.85)	< 0.00001	2.86 (2-3.87)	5.6 (4.33-6.06)	< 0.00001	2,83 (2.4-3.5)	4.67 (3.8-5.27)	< 0.00001
FeNO	38 (14-68)	29 (19-51)	0.011	29.5 (16-89)	32 (27-70)	NS	40 (10-59)	23.5 (8.5-46)	0.0048
FVC %	85 (70-97)	95.5 (78-104)	< 0.00001	86 (67-101)	98.5 (83-105)	0.0014	83.5 (70.5-96)	90.5 (76.5-102)	0,0003
FEV1 %	69 (53-82)	81,5 (65-92)	< 0.00001	71 (51-84)	82.5 (72-95)	0.0002	68 (54-76)	78.5 (63.5-91.5)	0.0001

Median (Interquartile range)