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SHORT COMMUNICATION

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Analysis of response of severe eosinophilic asthmatic patients to benralizumab

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corticosteroid intake;
exacerbations;
response analysis;
severe asthma

Abstract
Introduction: Clinical trials and real-life studies have been published showing effectiveness of benralizumab in severe eosinophilic asthmatic patients. The aim of the present study is to describe super-responders to benralizumab in a series of 79 patients who completed at least 1 year of treatment, and to compare super-responders with non super-responders.
Methods: This is a multicenter study of the Register of Severe Asthma of the Region of Murcia (RE-ASGRAMUR) Group performed in eight hospitals under the conditions of routine clinical practice. Patients with zero exacerbations and no oral corticosteroid therapy for asthma were

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considered super-responders. We analyzed clinical, functional, and inflammatory parameters of selected patients.
Results: In all, 50 of the 79 patients (63%) met the super-responder criteria. In addition, 36% of the patients (26/71) were considered as complete responders to treatment (super-responder + Asthma Control Test [ACT] ≥ 20 + forced expiratory volume in 1 s [FEV1] ≥ 80%). The super-responders were significantly older in age (P = 0.0029), had higher eosinophils count (P = 0.0423), higher proportion of nasal polyps (P = 0.036), and they had less severe disease at baseline. After 1 year of treatment, the super-responders had higher levels of ACT questionnaire (23 vs 19, P = 0.0007) and better percentage of FEV1 (83 vs 75, P = 0.0359).
Conclusion: Almost two of the three patients treated with benralizumab were super-responders after 1 year of treatment and 36% had a complete response. Super-responders were associated with older age, higher eosinophils count, had nasal polyposis as comorbidity, and had less severe disease at baseline. This data illustrated the good real-life response of patients with severe eosinophilic asthma to the treatment with benralizumab.

Introduction

Severe uncontrolled asthma is defined as the asthma that is controlled poorly despite treatment with a combination of high-dose inhaled corticosteroids and long-acting β2-agonists and/or other controller drugs in the past 1 year, or oral corticosteroids for at least 6 months during the same period. The prevalence of uncontrolled, severe, and persistent asthma has been estimated to be 3.9% of the asthmatic population.[1] Eosinophilic asthma is the most common asthmatic phenotype, accounting for over 50% of cases of severe asthma.

Benralizumab is a monoclonal antibody that binds the α-subunit of interleukin 5 (IL-5) receptor, leading to depletion of circulating peripheral blood eosinophils within the first 24 h. This effect persists for at least 2–3 months.[2]

Clinical trials SIROCCO[3] and CALIMA[4] have shown the efficacy and safety of benralizumab in patients with severe eosinophilic asthma. Real-life studies have also been published showing effectiveness of benralizumab.[5] We found benralizumab to be an effective treatment for patients with severe eosinophilic asthma, decreasing both number of exacerbations and intake of oral corticosteroids, and improving disease control, quality of life, and lung function values.[6]

Kavanagh et al. described super-responders to benralizumab as patients with zero exacerbation and no oral corticosteroid therapy for asthma.[7]

The aim of the present study was to describe super-responders in a series of 79 patients with severe eosinophilic asthma who had completed at least 1 year of benralizumab treatment, and to compare super-responders with non super-responders.

Method

This is a multicenter study of the Register of Severe Asthma of the Region of Murcia (RE-ASGRAMUR) Group performed in eight hospitals of the Region of Murcia (Spain) under conditions of routine clinical practice. The study was conducted ethically in accordance with the World Medical Association Declaration of Helsinki, and was approved by the Research Ethics Committee.

We analyzed clinical characteristics, eosinophilia, total immunoglobulin E (IgE), drug tolerance and effectiveness (exacerbations, Asthma Control Test [ACT], Asthma Quality of Life Questionnaire [mini AQLQ], lung function test [Forced Expiratory Volume in 1 s or FEV1, and Forced Vital Capacity or FVC]), and use of oral corticosteroids.

Patients with zero exacerbation and no oral corticosteroid therapy for asthma were considered as super-responders.[7]

An initial descriptive analysis of the studied variables was done; absolute frequencies and percentage values were used for qualitative variables, and median and interquartile range were used for quantitative variables. Chi-square test was applied to study association between qualitative variables. The normality of quantitative variables was studied with the Shapiro–Wilks Test, and a nonparametric Mann–Whitney U test was used to compare these variables between super-responders and non super-responders. For all comparisons, $P < 0.05$ was considered significant. Stata v15 program (College Station, TX) was used for data analysis.

Results

We presented a series of 79 patients diagnosed with severe eosinophilic asthma after completing at least 1 year of treatment with benralizumab, with a mean duration of treatment being 18.8 months. Initially, 84 patients were included in the Register; however five patients were excluded from the study as they did not complete 1 year of treatment because of adverse reactions: the first patient had local pain and asthenia, so refused treatment; the second patient had influenza-like syndrome; the third had headache; and the fourth and fifth stopped treatment due to arthralgia and bronchospasm plus headache, respectively. After 1 year of treatment with benralizumab, 50 of the 79 patients (63%) met the super-responder criteria. In addition to zero exacerbations and no intake of oral corticosteroids, 36% of the patients (26/71) had an ACT ≥ 20 and an FEV1 ≥ 80%; this being considered a complete response to treatment according to the Consensus Document of the Spanish Society of Pneumology and Thoracic Surgery (SEPAR).[8]

Twenty-nine patients were non super-responders: were non super-responders: 23 had at least one exacerbation during the year of treatment (11 patients had one exacerbation, three patients had two exacerbations, four patients had three exacerbations, and five patients had four or more exacerbations), with a mean of 2.6 exacerbations/year; 14 patients continued with oral corticosteroids with a mean dose of 11.4 mg/day.

Considering baseline characteristics of the patients (Table 1), super-responders were significantly older in age than non super-responders, had higher count of eosinophils, higher ACT and mini AQLQ questionnaires scores, and had a higher proportion of nasal polyps (48% vs 24%). The percentage of patients with >500 eosinophils was higher among super-responders (70%) than the rest (44%) of patients. A higher proportion of patients were cortico-dependent among non super-responders, although not statistically significant. These patients took significantly higher dose of oral corticosteroids (15 mg/day) than super-responders (6.75 mg/day).

Considering disease control, super-responders had significantly higher ACT scores (23 vs 19), with 73% presenting a score of ≥20 after 1 year of treatment (Table 2). They also had higher mini AQLQ questionnaire scores, although not statistically significant. Super-responders also had

Table 1 Baseline features of super-responders versus non super-responders.

Variable	Super-responders N 50 (63.3%)	Non super-responders N 29 (36.7%)	P
Females n (%)	26 (52)	20 (69)	0.141 NS
Age (y)	64.4 (55.9-71.5)	51.4 (45.8-65.2)	**0.0029**
Age at onset of			0.078 NS
symptoms	7 (14.9)	9 (32.1)	
0-18 years n (%)	40 (85.1)	19 (67.9)	
>18 years n (%)			
Disease evolution (y)	17.14 (10.8-27.5)	22.8 (14.2-36.6)	0.3887 NS
BMI	29.5 (26-34.6)	28 (23.3-33.8)	0.2324 NS
Atopy n (%)	19 (38)	12 (41.4)	0.767 NS
Smoking			0.414 NS
Never smoker, n (%)	28 (56)	13 (44.8)	
Ex-smoker, n (%)	21 (42)	14 (48.3)	
Smoker, n (%)	1 (2)	2 (6.9)	
Eosinophils	670 (400-900)	470 (250-700)	**0.0423**
Eosinophils > 500, n (%)	35 (70)	13 (44)	**0.027**
IgE	129 (56-340)	130.5 (47.5-418)	0.9551 NS
FeNO	38 (16-68)	24 (10-56)	0.3620 NS
Nasal polyps n (%)	24 (48)	7 (24.1)	**0.036**
Exacerbations	3 (2-5)	4 (3-7)	**0.0165**
Oral corticosteroids,	20 (40)	18 (62)	0.0584 NS
mg/day, n (%)	6.75 (4.5-10)	15 (10-30)	**0.0133**
ACT	14 (8-17)	11 (8-13)	**0.0481**
AQLQ	2.87 (2.67-3.87)	2.67 (2.27-2.86)	**0.0492**
FEV1 (%)	71 (58-82)	62 (47-82)	0.2030 NS
FVC (%)	85 (74-98)	87 (64-100)	0.7507 NS
FEV1/FVC	0.69 (0.63-0.75)	0.67 (0.58-0.72)	0.4069 NS

Data are presented as n (%) or median (interquartile range).
BMI: body mass index; IgE: immunoglobulin E; FeNO: fractional exhaled nitric oxide.

Table 2 Results of super-responders versus non super-responders.

Variable	Super-responders	Non super-responders	P
ACT	23 (20-24)	19 (15-22)	**0.0007**
ACT ≥ 20, n (%)	33/45 (73)	11/27 (41)	**0.006**
AQLQ	5.1 (4.3-6)	4.5 (3.5-5.7)	0.0975 NS
FVC (%)	96 (83-102)	98 (66-108)	0.6114 NS
FVC (%) ≥80, n (%)	39/48 (81)	19/29 (65)	0.080 NS
FEV1 (%)	83 (74-96)	75 (58-92)	**0.0359**
FEV1 (%) ≥80, n (%)	30/48 (62)	11/29 (38)	**0.036**
FEV1/FVC	0.72 (0.65-0.78)	0.67 (0.62-0.74)	0.1029 NS
FEV1/FVC ≥ 0.7, n (%)	27/48 (56)	10/29 (34)	0.064 NS

Data are presented as n (%) or median (interquartile range).

significantly better FEV1 (83% vs 75%), and 62% of them had an FEV1 ≥ 80%. We found no significant difference in FVC and FEV1/FVC percentage scores.

Discussion

We want to highlight that almost two out of three patients who had completed 1 year of benralizumab treatment did not present exacerbations or used systemic corticosteroids during the period of treatment, fulfilling the criteria of being super-responders. These estimates were higher than 39% reported by Kavanagh et al..[7] One of every three patients, in addition to meeting the definition of super-responder, presented an ACT ≥ 20 and an FEV1 ≥ 80%, being considered a complete response.[8]

Considering the baseline factors associated with being a super-responder, we found older age, higher count of eosinophils, and nasal polyposis as comorbidity. The last two factors were described as associated with a greater response to benralizumab in a pooled analysis of the SIROCCO and CALIMA studies.[9]

In our series, similar to the results published by Kavanagh et al.,[7] super-responders had less severe disease at baseline, when compared to nonresponders, with better ACT and mini AQLQ scores, fewer exacerbations, and less dose of oral corticosteroids. It is perceived that patients with milder disease may meet super-responder criteria more easily than those with more severe disease.

Presence of atopy was not associated with a greater response to benralizumab, which is consistent in a *post hoc* analysis assessing the influence of atopy on benralizumab efficacy, demonstrating that patients with severe eosinophilic asthma treated with benralizumab had consistent reduction in risk of exacerbation, regardless of IgE concentrations.[10]

After 1 year of treatment, super-responders had ACT = 23, clearly above the level of good control (score of 20). Of note, three out of four super-responders had ACT ≥ 20. These asthma control data were significantly better in super-responders compared to other patients.

Considering FEV1%, the median proportion of in super-responders was 83%, with almost two out of three patients presenting a normal FEV1 percentage (≥80%), reaching statistically significant differences with no super-responders.

Although there were no statistically significant differences with non super-responders in FVC%, 81% of super-responders had FVC ≥ 80%, illustrating good lung function data in these patients after benralizumab treatment.

Conclusion

Almost two out of three patients treated with benralizumab were super- responders (free of exacerbations and corticosteroid use) after 1 year of treatment, asthma in 73% of patients was well controlled, and 62% had normal FEV1% score. In addition, 36% of patients met the complete response criteria of SEPAR, with no exacerbations, no use of oral corticosteroids, ACT ≥ 20, and FEV1 ≥ 80%. The data illustrated good response of severe eosinophilic asthmatic patients to benralizumab treatment.

Conflict of Interest Statement

Juan Carlos Miralles-López received consultancy fees from Chiesi and speaker fees from Novartis, GSK, Astra Zeneca, Sanofi, and Chiesi. Rubén Espinosa-Andújar received speaker fees from Novartis, GSK, Astra-Zeneca, Sanofi, and Chiesi. Francisco Javier Bravo-Gutiérrez received speaker fees from Novartis, Ferrer, GSK, Astra-Zeneca, Sanofi, and Chiesi. Manuel Castilla-Martínez received consultancy fees from GSK and Astra Zeneca and speaker fees from Novartis, GSK, Astra-Zeneca, Sanofi, and Chiesi. Isabel María Flores-Martín received speaker fees from Novartis, GSK, and Sanofi. María Loreto Alemany-Francés received speaker fees from Novartis, GSK, Astra-Zeneca, and Chiesi. Manuel José Pajarón-Fernández received speaker fees from GSK. Sheila Cabrejos-Perotti received speaker fees from Sanofi. Zouhair El-Molaka received speaker fees from Astra-Zeneca, Teva, and GSK. José Meseguer-Arce received speaker fees from GSK. María Jesús Avilés-Inglés received speaker fees from Chiesi. José Valverde-Molina 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. Finally, Ana Mora-González and Virginia Pérez-Fernández had no conflicts of interest to declare.

Author Contributions

Juan Carlos Miralles-López, Rubén Andújar-Espinosa, Francisco Javier Bravo-Gutiérrez, Manuel Castilla-Martínez, Isabel Flores-Martín, María Loreto Alemany-Francés, Manuel José Pajarón-Fernández, Ana Mora-González, Sheila Cabrejos-Perottimade, Zouhair El-Molakamade, José Meseguer-Arce, María Jesús Avilés-Inglés, José Valverde-Molina, and Virginia Pérez-Fernández made substantial contributions to the study, planning, and design, data collection and analysis, interpretation of results, drafting and revising of the manuscript, and reading and approving the final submitted version of the manuscript.

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Appendix: Members of the Register of Severe Asthma of the Region of Murcia Group

REgistro de ASma GRAVE de la Región de MURcia (RE-ASGRAMUR)

Steering Group

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