

First-Line Versus Second-Line Use of Reslizumab in Severe Uncontrolled Asthma

Pérez de Llano LA^{1*}, Cosío BG^{2,3,4*}, Lobato Astiárraga I⁵, Soto Campos G⁶, Tejedor Alonso MA⁷, Marina Malanda N⁸, Padilla Galo A⁹, Urrutia Landa I¹⁰, Michel de la Rosa FJ¹¹, García-Moguel I¹², on behalf of the Reslizumab Real-Life Spanish group**

¹Pulmonology Department, Hospital Lucus Augusti, Lugo, Spain

²Pulmonology Department, Hospital Universitario Son Espases, Illes Balears, Spain

³Instituto de Investigación Sanitaria Islas Baleares (IdISBa), Palma de Mallorca, Spain

⁴CIBER de enfermedades respiratorias (CIBERES), Madrid, Spain

⁵Pulmonology Department, Complejo Asistencial de Ávila, Ávila, Spain

⁶Pulmonology and Allergy Unit, University Hospital of Jerez, Jerez de la Frontera, Cádiz, Spain

⁷Allergy Unit, Hospital Universitario Fundación Alcorcón, Madrid, Spain

⁸Pulmonology Department, Hospital Universitario de Cruces, Barakaldo, Bizkaia, Spain

⁹Pulmonology Department, Hospital Costa del Sol, Marbella, Málaga, Spain

¹⁰Respiratory Medicine Department, Galdakao Hospital, Galdakao, Bizkaia, Spain

¹¹Pulmonology Department, Hospital Universitario Donostia, San Sebastián, Spain

¹²Department of Allergy, Hospital Universitario 12 de Octubre, Madrid, Spain

*Co-primary authors

**The full list of the Reslizumab real-life Spanish group is included in the appendix.

J Investig Allergol Clin Immunol 2023; Vol. 33(3): 220-222
doi: 10.18176/jiaci.0839

Key words: Eosinophilic asthma. Reslizumab. Asthma control. Monoclonal antibodies.

Palabras clave: Asma eosinofílica. Reslizumab. Control del asma. Anticuerpos monoclonales.

We recently showed reslizumab to be an effective therapy for uncontrolled severe eosinophilic asthma (USEA) in real-life conditions, achieving a complete response leading to asthma control (defined as absence of severe exacerbations, Asthma Control Test [ACT] score ≥ 20 , and no maintenance oral corticosteroids [OCS]) in 40% of the patients analyzed [1]. Given that many biologic-treated USEA patients do not achieve complete control [2], monoclonal antibodies can be prescribed in 2 different clinical scenarios: in patients not previously exposed to these drugs (first line, FL) and in patients with prior failure to a different drug (second line, SL). Reslizumab has previously proven to be an effective option for patients whose therapy with omalizumab fails [3], and other biologics have

also proven beneficial when one is switched to another [4-6]. However, to the best of our knowledge, no previous studies have investigated whether the response is similar or different when given as FL or SL.

We performed a multicenter, retrospective, real-life study of patients with USEA who had completed a 52-week treatment period with reslizumab in 44 reference asthma units throughout Spain. Our objectives were to compare the effectiveness of the drug between 91 FL patients and 68 SL patients after 52 weeks of treatment and to identify clinical factors associated with response in SL drugs. The main outcome was the percentage of patients with a complete response leading to asthma control, defined as the absence of severe exacerbations, ACT ≥ 20 , and no maintenance OCS. Secondary outcomes included the number of severe exacerbations, OCS dose, ACT score, FEV₁, FeNO, and FEOS score (which assigns relative weights to 4 domains [FEV₁, exacerbations, OCS, and symptoms] to quantify changes in patients' clinical condition after starting a biologic treatment) [7].

The statistical analysis was performed using IBM SPSS 23.0 (IBM Corp). Categorical variables were expressed as numbers and percentages and quantitative variables as mean (SD) if normally distributed or median (IQR) if nonnormally distributed, unless otherwise indicated. Comparisons between groups were performed using the χ^2 or Fisher exact test for categorical data, the *t* test for independent samples, and the Mann-Whitney test for continuous data. Univariate and multiple logistic regression were applied to establish the relationships between several independent variables. A more detailed description of the statistical method used is provided in the supplementary material.

The study population comprised 159 patients. Sixteen out of 68 SL patients had received mepolizumab (6 had not responded to omalizumab) and 52 had received omalizumab. At baseline, a positive skin prick test result was more frequent in SL than in FL patients. No other statistically significant differences were found between the groups (Table S1).

We found that, after 52 weeks of treatment with reslizumab, a considerable percentage of both FL and SL patients had achieved a complete response leading to asthma control (46% vs 32.4%; *P*=.086), with a higher ACT score in FL patients (20.9 vs 18.8; *P*=.015) and more patients achieving a clinically meaningful response in this group (Table).

Both groups experienced a significant improvement in clinical and functional outcomes after 52 weeks of therapy with reslizumab (Table S2). Of note, the magnitude of the response achieved (comparing baseline and endline clinical status using the FEOS score) was greater in FL patients than in SL patients, almost reaching statistical significance. Of note, the celerity of response did not differ between the groups and was largely achieved at 6 months (Table S3).

The results of the univariable analysis are shown in Table S4: a higher number of exacerbations in the preceding year, lower ACT score, and maintenance OCS at baseline were risk factors for not achieving control. In the multivariate analysis, SL patients with ACT >14 at baseline were more likely to achieve asthma control than those with ACT ≤ 10 (OR, 8.786 [95%CI, 1.975-39.292]; *P*=.004), whereas SL patients who were receiving maintenance OCS prior to starting reslizumab

Table. Clinical Outcomes After 1 Year of Treatment With Reslizumab: Comparison Between First-Line and Second-Line Groups.

Variable	Total (n=159)		First-line (n=91)		Second-line (n=68)		P Value
Complete asthma control after 1 y of reslizumab treatment, No. (%)	62	40.0%	40	46.0%	22	32.4%	.086
Patients with exacerbations, No. (%)	37	23.7%	18	20.5%	19	27.9%	.276
Median (IQR) no. of exacerbations ^a	1	1-2	1	1-2	1	1-2	.343
Mean (SD) ACT	20.0	5.1	20.9	4.5	18.8	5.7	.015
ACT \geq 20, No. (%)	100	64.5%	61	70.1%	39	57.4%	.099
Mean (SD) ACT increase from baseline	7.1	5.3	7.8	5.0	6.2	5.6	.019
ACT increase from baseline \geq 3, No. (%)	122	78.7%	73	83.9%	49	72.1%	.074
OCS maintenance therapy, No. (%)	30	19.0%	13	14.4%	17	25.0%	.094
Median (IQR) OCS burden, mg prednisone eq/d ^b	6.2	3.4-10.4	5.8	2.1-12.3	7.2	3.8-10.1	.811
Mean (SD) FEOS score	76.4	22.3	79.7	22.6	72.3	21.3	.060

Abbreviations: ACT, Asthma Control Score; FEOS, FEV₁, Exacerbations, Oral corticosteroids, Symptoms); OCS, oral corticosteroids.

^aIn 37 patients who presented an exacerbation in the first year of therapy with reslizumab.

^bIn 30 patients who used OCS in the first year of therapy with reslizumab.

were less likely to achieve control than those who were not treated with long-term OCS (OR, 0.988 [95%CI, 0.977-0.999]; $P=.038$). This contrasts with previously reported results, where OCS-dependent patients achieved greater improvements than the overall population [8]. It could be hypothesized that USEA patients who did not previously respond to a monoclonal antibody and were OCS-dependent represent a more refractory population, owing to more eosinophilic inflammation or to the relevant participation of other alternative or complementary inflammatory pathways (eg, IL-4/IL-13, T1, T3).

This study is limited by the number of patients and the consequences of the observational retrospective cohort study design. Another limitation is that most SL patients had been receiving omalizumab, although it should be noted that 16 switched from another anti-IL-5 drug (mepolizumab). We found that the response to reslizumab was greater in patients with previous failure to omalizumab than to mepolizumab, although the latter also improved (Table S5). In fact, mean (SD) FEOS was 73.6 (23.3) in patients who had been receiving omalizumab and 68.2 (13.3) in those who had been receiving mepolizumab ($P=.283$). Although the results were better in the first group (maybe reflecting more potential for improvement when the switch drug targets an alternative inflammatory subpathway), the small sample of SL patients does not enable us to draw relevant conclusions. Failure to respond to mepolizumab is probably related to the low drug concentrations achieved in the airways and associated local autoimmunity [9], a drawback that could be avoided with the use of reslizumab, which is adjusted for body weight.

Although a higher proportion of USEA patients who initiate reslizumab for the first time achieved control of their asthma, the results are not negligible in SL: control was achieved in 32%, a percentage that differs little from those reported in other studies that included a nonselected sample [2]. Further studies

are necessary to provide more conclusive data on response to monoclonal antibodies in SL therapy and to find reliable predictors of response.

Acknowledgments

The authors would like to thank Dr Marta Villarnovo and BRINDA Healthcare for their assistance with the logistics of data collection and analysis.

Funding

This project was supported by the Integrated Asthma Research Program of the Spanish Respiratory Society (PII de asma SEPAR), which played no role in the analysis, decision to publish, or preparation of the manuscript. The design, analysis, and writing of this report are entirely the work and responsibility of the authors, and Dr Cosío and Dr Pérez de Llano had full access to all data and final responsibility for the decision to submit this work for publication.

Conflicts of Interest

Luis Perez de Llano has received grants and/or fees for consultancy or speaking from Novartis, AstraZeneca, GSK, Teva, Boehringer-Ingelheim, Chiesi, Sanofi, Menarini, Mundipharma, and Esteve. Borja G Cosío has received speaking or advisory fees or financial assistance to attend congresses from AstraZeneca, GSK, Novartis, Chiesi, Mundipharma, Menarini, TEVA, Boehringer-Ingelheim, and Rovi. Ignacio Lobato Astiárraga has received speaker fees and consulting fees from AstraZeneca, GlaxoSmithKline, Novartis, Chiesi, Sanofi, Boehringer, and Teva. Gregorio Soto Campos has received speaker fees and consulting fees from ALK, AstraZeneca, Bial, Boehringer-Ingelheim,

Chiesi, GlaxoSmithKline, Novartis, Sanofi, and Teva. Miguel Ángel Tejedor Alonso declares that he has no conflicts of interest. Nuria Marina Malanda has received speaker fees and consulting fees from AstraZeneca, Sanofi, GlaxoSmithKline, Chiesi, Pfizer, Novartis, and Teva. Alicia Padilla Galo has received speaking or advisory fees or financial assistance to attend congresses from Novartis, Teva, AstraZeneca, GlaxoSmithKline, and ALK. Isabel Urrutia Landa has received speaking or advisory fees or financial assistance to attend congresses from AstraZeneca, Sanofi, GlaxoSmithKline, Chiesi, Bial Aristegui, Teva, Novartis, ALK, Boehringer-Ingelheim, and Mundi Pharma. Francisco Javier Michel de la Rosa has received speaker fees and/or consulting fees and/or support to attend congresses from AstraZeneca, Boehringer-Ingelheim, Chiesi, CSL Behring, GlaxoSmithKline, Grifols, Novartis, Sanofi Aventis, and Teva. Ismael García-Moguel has received speaking or advisory fees or financial assistance to attend congresses from AstraZeneca, Sanofi, GlaxoSmithKline, Chiesi, Mundipharma, Allergy Therapeutics, Novartis, Stallergenes Greer, and Teva.

Corticosteroid-Dependent Asthma. *J Allergy Clin Immunol Pract.* 2020;8(2):555-64.

9. Mukherjee M, Aleman Paramo F, Kjarsgaard M, Salter B, Nair G, LaVigne N, et al. Weight-adjusted Intravenous Reslizumab in Severe Asthma with Inadequate Response to Fixed-Dose Subcutaneous Mepolizumab. *Am J Respir Crit Care Med.* 2018;197(1):38-46

■ *Manuscript received April 8, 2022; accepted for publication June 23, 2022.*

Borja G Cosío

Department of Respiratory Medicine
Hospital Universitario Son Espases-IdISBa
Palma de Mallorca, Spain
E-mail: borja.cosio@ssib.es

References

1. Pérez de Llano LA, Cosío BG, Lobato Astiárraga I, Soto Campos G, Tejedor Alonso MÁ, Marina Malanda N, et al. Asthma Control in Patients with Severe Eosinophilic Asthma Treated with Reslizumab: Spanish Real-Life Data. *J Asthma Allergy.* 2022;15:79-88.
2. Bhalla A, Zhao N, Rivas DD, Ho T, Perez de Llano L, Mukherjee M, et al. Exacerbations of Severe Asthma While on Anti-IL-5 Biologics. *J Investig Allergol Clin Immunol.* 2020;30(5):307-16.
3. Pérez de Llano LA, Cosío BG, Domingo C, Urrutia I, Bobolea I, Valero A, et al. Efficacy and Safety of Reslizumab in Patients with Severe Asthma with Inadequate Response to Omalizumab: A Multicenter, Open-Label Pilot Study. *J Allergy Clin Immunol Pract.* 2019;7(7):2277-83.
4. Kavanagh JE, Hearn AP, d'Ancona G, Dhariwal J, Roxas C, Green L, et al. Benralizumab after sub-optimal response to mepolizumab in severe eosinophilic asthma. *Allergy.* 2021;76(6):1890-3.
5. Chapman KR, Albers FC, Chipps B, Muñoz X, Devouassoux G, Bergna M, et al. The clinical benefit of mepolizumab replacing omalizumab in uncontrolled severe eosinophilic asthma. *Allergy.* 2019;74(9):1716-26.
6. Mümmler C, Munker D, Barnikel M, Veit T, Kayser MZ, Welte T, et al. Dupilumab Improves Asthma Control and Lung Function in Patients with Insufficient Outcome During Previous Antibody Therapy. *J Allergy Clin Immunol Pract.* 2021;9(3):1177-85.
7. Pérez de Llano L, Dávila I, Martínez-Moragón E, Domínguez-Ortega J, Almonacid C, Colás C, et al. Development of a Tool to Measure the Clinical Response to Biologic Therapy in Uncontrolled Severe Asthma: The FEV1, Exacerbations, Oral Corticosteroids, Symptoms Score. *J Allergy Clin Immunol Pract.* 2021;9(7):2725-31.
8. Nair P, Bardin P, Humbert M, Murphy KR, Hickey L, Garin M, et al. Efficacy of Intravenous Reslizumab in Oral