

First line versus second line use of reslizumab in severe uncontrolled asthma

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We have recently shown that reslizumab is an effective therapy for severe eosinophilic uncontrolled asthma (SEUA) in real-life conditions, achieving a complete response leading to asthma control -defined as absence of severe exacerbations, ACT \geq 20 and no maintenance oral corticosteroids (OCS)- in 40% of the analyzed patients [1]. Given the fact that many biologic-treated SEUA patients do not achieve complete control [2], monoclonal antibodies can be prescribed in two different clinical scenarios: in patients not previously exposed to these drugs (first line: FL) or in patients with a prior failure to a different one (second line: SL). Reslizumab has previously demonstrated to be an effective option for patients with failure to omalizumab [3] and other biologics have also shown benefit in switching from one to another [4, 5, 6]. However, to the best of our knowledge, it has never been investigated whether the response is similar or different when given as FL or SL.

The aim of this multi-centre, retrospective, real-life study that included subjects with SEUA who had completed a 52-week treatment period with reslizumab in 44 asthma units of reference throughout Spain, was to compare its effectiveness between 91 FL patients and 68 SL patients after 52 weeks of treatment and to identify clinical factors associated to response in SL. The main outcome was percentage of patients with complete response leading to asthma control, defined as absence of severe exacerbations, ACT \geq 20 and no maintenance OCS. Secondary outcomes included number of severe exacerbations, OCS dose, Asthma Control Test (ACT) score, FEV₁, FeNO and FEOS score (this score assigns relative weights to four domains: FEV₁, exacerbations, OCS and symptoms to quantify changes in patients' clinical condition after starting a biologic treatment) [7].

Statistical analysis was performed using IBM SPSS 23.0 (Armonk, NY; USA). Categorical variables were stated as numbers (n) and percentages (%) and quantitative variables as mean \pm standard deviation (SD) if normally distributed or median and interquartile range (IQR) if non-normally distributed unless otherwise indicated. Comparisons between groups were performed using Chi-squared or Fisher's exact test for categorical data and Student's t-test for independent samples or Mann-Whitney-U-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.

One hundred and fifty-nine patients were included. Sixteen out of 68 SL patients came from mepolizumab (6 of them had previously failed to respond to omalizumab) and 52 came from omalizumab. At baseline, positive skin prick-test was more frequent in SL than in FL patients. No other statistically significant differences were found between groups (table S1).

We found that, after 52 weeks of treatment with reslizumab, a considerable proportion of both FL and SL patients achieved a complete response leading to asthma control (46% vs 32.4%; $p = 0.086$), with higher ACT score in FL patients (20.9 vs 18.8; $p = 0.015$) and more patients reaching clinically meaningful in this group (table 1).

Both groups showed a significant improvement in clinical and functional outcomes after 52 weeks of reslizumab therapy when compared to their situation before the initiation of this therapy (table S2). It must be noted that the magnitude of the response achieved (comparing baseline and endline clinical status by using the FEOS score) was greater in FL patients than in SL, nearly reaching statistical significance. Of note, the celerity of response was not different between both groups, and it was largely achieved at 6 months (table S3).

Univariable study results are shown in table S4: a higher number of exacerbations in the preceding year, lower ACT and maintenance OCS at baseline have been shown to be risk factors for not achieving control. In multivariate analysis, SL patients with $ACT > 14$ at baseline were more likely to achieve asthma control than those with $ACT \leq 10$, OR 8.786 (CI95%: 1.975 – 39.292; $p = 0.004$), whereas SL patients who were receiving maintenance OCS prior to reslizumab initiation were less likely to gain control than those who were not treated with chronic OCS, OR 0.988 (CI95%: 0.977 – 0.999; $p = 0.038$). This is in contrast with previously reported results, where OCS-dependent patients achieved greater improvements than the overall population [8]. It could be hypothesized that SEUA patients with a history of failure to respond to a previous monoclonal antibody and OCS-dependence represent a more refractory population, due either to a more eosinophilic inflammation or to the relevant participation of other alternative or complementary inflammatory pathways (i.e., 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 came from omalizumab, but it should be noted that 16 patients 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 coming from omalizumab and 68.2 (13.3) from mepolizumab ($p = 0.283$). Although results were better in the first group (maybe reflecting more improvement potential when the switch drug targets an alternative inflammatory sub-pathway) the small sample of SL patients does not allow relevant conclusions. It has been published that failure to respond to mepolizumab is probably related to low drug concentrations achieved in the airways and associated local autoimmunity [9], a drawback that could be avoided with the use of reslizumab, a body weight-adjusted drug.

Although a higher proportion of SUEA patients who initiate reslizumab for the first time achieved asthma control, the results are not negligible in SL: 32% gained control, a percentage not different from other studies that included a non-selected sample [2]. Further studies are necessary to provide more conclusive data on response to monoclonal antibodies in SL and to find reliable predictors of response.

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.

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Conflict of interest

Luis Perez de Llano declares to have received grants and/or fees for consultancy or speeches from Novartis, Astra-Zeneca, GSK, Teva, Boehringer-Ingelheim, Chiesi, Sanofi, Menarini, Mundipharma, and Esteve. Borja G Cosío declares he has received speaking or advisory fees, or economic aid to attend congresses from Astra-Zeneca, GSK, Novartis, Chiesi, Mundipharma, Menarini, TEVA, Boehringer-Ingelheim, and Rovi. Ignacio Lobato

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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 |
|---|------------------|----------|----------------------|----------|-----------------------|----------|-------|
| Complete asthma control after 1 year of reslizumab treatment (n, %) | 62 | 40.0% | 40 | 46.0% | 22 | 32.4% | 0.086 |
| Patients with exacerbations (n, %) | 37 | 23.7% | 18 | 20.5% | 19 | 27.9% | 0.276 |
| Number of exacerbations (median, IQR) ^A | 1 | 1-2 | 1 | 1-2 | 1 | 1-2 | 0.343 |
| ACT (mean, SD) | 20.0 | 5.1 | 20.9 | 4.5 | 18.8 | 5.7 | 0.015 |
| ACT ≥ 20 (n, %) | 100 | 64.5% | 61 | 70.1% | 39 | 57.4% | 0.099 |
| ACT increase from baseline (mean, SD) | 7.1 | 5.3 | 7.8 | 5.0 | 6.2 | 5.6 | 0.019 |
| ACT increase from baseline ≥ 3 (n, %) | 122 | 78.7% | 73 | 83.9% | 49 | 72.1% | 0.074 |
| OCS maintenance therapy (n, %) | 30 | 19.0% | 13 | 14.4% | 17 | 25.0% | 0.094 |
| OCS burden (mg prednisone eq./day) (median, IQR) ^B | 6.2 | 3.4-10.4 | 5.8 | 2.1-12.3 | 7.2 | 3.8-10.1 | 0.811 |
| FEOS score (mean, SD) | 76.4 | 22.3 | 79.7 | 22.6 | 72.3 | 21.3 | 0.060 |

^A : In 37 patients who presented some exacerbation in the first year with reslizumab

^B: In 30 patients who used OCS in the first year with reslizumab