

REDES study: Mepolizumab is effective in patients with severe asthma and comorbid nasal polyps

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More than nine out of every ten patients with Severe Asthma (SA) with eosinophilic phenotype suffer from comorbid diseases (1). Of these, Chronic Rhinosinusitis with Nasal Polyps (CRSwNP) is among the most common reported comorbidities, with up to 46.2% of patients impacted by upper airway inflammation (2). Between 10% and 30% of patients with mild asthma have also CRSwNP, this incidence increases to 70% to 90% in severe asthma (3).

Several biologics approved for severe asthma have shown their benefits in patients with comorbid nasal polyps in clinical trials, showing an enhanced response in this subgroup of patients (4, 5). The REDES study was a real-world, observational, retrospective, multicentric study of the effectiveness and safety of mepolizumab 100 mg SC Q4W in Spain for 12 months. 318 SA patients were included in the study, of which 147 had comorbid CRSwNP. Briefly, key inclusion criteria were a diagnosis of SA with eosinophilic phenotype in patients aged ≥ 18 years, having initiated mepolizumab at least 12 months prior to the inclusion in the study, and having at least 12 months of key clinical information available before mepolizumab initiation (2).

We conducted a post hoc analysis of the REDES study to evaluate the effectiveness of mepolizumab according to the presence or absence of comorbid CRSwNP. We analysed the change after 12 months of the annual number of exacerbations, the improvement in asthma control as per the Asthma Control Test (ACT), the change in maintenance Oral Corticosteroids (OCS) use, the change in lung function measured as pre-bronchodilator Forced Expiratory Volume at 1 s (FEV_1), and blood eosinophil counts. Baseline demographic features were also compared between the groups. Two-tailed T-tests were carried out for comparisons of continuous variables intragroup (paired) and intergroup (unpaired).

The baseline characteristics were overall similar across both subgroups of patients (**Table 1**), with no significant differences apart from the blood eosinophil counts at baseline, which were slightly higher: mean (SD) of 798.78 (923.26) cells/ μ l in patients with CRSwNP, compared with 633.54 (748.5) cells/ μ l without CRSwNP ($p=0.04$). After 12 months, both cohorts reduced their eosinophils to normal concentrations: 77.38 (58.18) cells/ μ l and 115.67 (314.32) cells/ μ l. OCS maintenance dose was also different at baseline 14.31 mg/day in those without CRSwNP vs 9.48 mg/day with CRSwNP ($p=0.0163$).

The exacerbation reduction at 12 months was 83.4% in patients with comorbid CRSwNP, from a mean (SD) of 4.33 (3.55) to 0.73 (1.14) exacerbations/year, compared with a 73.0% reduction in those without CRSwNP, from 4.60 (3.49) to 1.24 (1.61) exacerbations/year post mepolizumab (intergroup $p=0.0017$). 53.7% of patients with nasal polyps, and 42.9% of patients without nasal polyps, were able to withdraw their maintenance OCS at 12 months. Those with CRSwNP increased their ACT score from a mean (SD) 14.63 (5.16) to 21.09 (3.72) after 12 months

($p < 0.01$), achieving $ACT \geq 20$ in 76.0% of them, compared with 69.8% of patients without nasal polyps, who also increased their mean ACT score from 13.57 (4.90) at baseline to 20.60 (3.98) ($p < 0.01$). Pre-BD FEV_1 improved in both cohorts by 0.18 L and 0.23 L, and z-scores changed from -2.04 and -2.11 to -1.54 and -1.61 with and without comorbid NP, respectively. The different FEOS scores were calculated where data was available, showing slightly higher scores in patients with NP (table S1)(6, 7). Recently published real-world studies show consistent results in terms of exacerbation reduction, OCS use and overall response in patients with comorbid NP in real life, compared with severe asthma patients without NP (8)

The concept of unified airway disease highlights the relationship between inflammatory mechanisms of upper airway disease (chronic rhinosinusitis with or without nasal polyps) and lower airway disease (9). CRSwNP usually have more impact on asthma burden of disease than other comorbidities: longer duration of nasal symptoms, poorer health-related quality of life, and greater exposure to systemic corticosteroids (3, 10).

Eosinophils and the overexpression of IL-5, play a critical role in the pathogenesis of severe asthma and CSRwNP, stimulating on one side, the cysteinyl leukotriene pathway related to nasal congestion, rhinorrhea and loss of smell, and on the other side, contributing to the prostaglandin D2 signaling, responsible for smooth muscle contraction and bronchoconstriction (11). They are involved in tissue remodeling, airway hyperresponsiveness, epithelial integrity, mucus viscosity, among others (12, 13). Therefore, inhibiting the IL5 pathway may reduce the overlapping symptoms for both pathologies leading to an overall better disease control. Mepolizumab is the only anti IL-5 approved by the FDA and EMA for SA with eosinophilic phenotype, CRSwNP, as well as for the systemic eosinophilic diseases EGPA and HES. Treatment with mepolizumab could therefore present a concomitant benefit in the upper and lower respiratory tract on patients with SA and comorbid NP as described in recent literature examples (4, 14). Biologic therapy for SA has the difficult challenge of achieving improvements both in the key problems of asthma and also its comorbidities, especially of concomitant nasal polyps (15, 16). A multidisciplinary approach in these patients, between respiratory physicians, allergists and ENT specialists is essential for an adequate diagnosis and treatment.

The main limitation of our work is that this was a post-hoc analysis of a retrospective real world study, and as such, we couldn't incorporate data that wasn't previously collected in the REDES study (e.g. nasal outcomes), and potential bias due to missing data may have been incorporated into these results, however these results come from one of the largest cohorts where the effectiveness and safety of mepolizumab have been assessed, and they are consistent with previous clinical trials and real world studies that suggest that patients with severe asthma and comorbid nasal polyps constitute a phenotype which appears to respond particularly well to mepolizumab in the real life setting.

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Conflicts of interest statement

- EA reports honoraria from lectures, presentations, speakers bureaus, manuscript writing or educational events from GSK, AstraZeneca, Chiesi, GebroPharma, Sanofi and Merck, support for attending meetings from GSK, AstraZeneca, Chiesi and Sanofi, and receipt of equipment materials, drugs, medical writing, gifts or other services from GSK, Chiesi and Merck.
- CC reports grants or contracts from AstraZeneca, Chiesi, GSK, Novartis and Sanofi, consulting fees from AstraZeneca, GSK, Novartis and Sanofi, payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from AstraZeneca, Chiesi, GSK, Mundipharma, Novartis, Pfizer and Sanofi, payment for expert testimony from AstraZeneca, Chiesi, GSK, Novartis and Sanofi, support for attending meetings and/or travel from Chiesi, GebroPharma, Mundipharma, Pfizer and Sanofi, participation on Data Safety Monitoring Board or Advisory Board with AstraZeneca, GSK, Novartis and Sanofi, and receipt of equipment, materials, drugs, medical writing, gifts or other services from GSK and Sanofi.
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- EMM reports consulting fees from AstraZeneca, GSK, Sanofi and Teva, and Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from AstraZeneca, Chiesi, Gebro, GSK, Novartis, Sanofi and Teva.
- SQ reports consulting fees from GSK, Sanofi and AstraZeneca, and honoraria from lectures, presentations, speakers bureaus, manuscript writing or educational events from GSK, AstraZeneca, Novartis, Chiesi, Mundipharma, Sanofi and Teva
- MGSB was an employee of GSK when this manuscript was written, and holds shares in GSK.
- DBC and ALM are employees of GSK and hold stocks/shares in GSK.

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TABLE LEGENDS

Table 1. Mepolizumab effectiveness according to the presence or absence of NP.

Demographic features	Valid n	Severe asthma without NP (n= 171)			Valid n	Severe asthma with NP (n=147)		
Age, years mean (SD)	171	56.74 (13.43)			147	56.33 (11.36)		
Age at diagnosis years mean (SD)/median	159	34.69 (18.95)/37			142	33.37 (16.68)/32.5		
Sex, female, n (%)	171	130 (76.0%)			147	90 (61.2%)		
BMI kg/m ² mean (SD)	170	29.37 (5.75)			146	27.67 (5.05)		
Non-smoker, n (%)	171	116 (67.8%)			147	82 (55.8%)		
Exsmoker n (%)	171	48 (28.1%)			147	58 (39.5%)		
Atopic sensitization (n, %)	171	80 (46.78%)			145	51 (35.17%)		
Clinical outcomes	Valid n	Baseline	12 months	P value	Valid n	Baseline	12 months	P value
Blood eosinophil counts, mean (SD)	171	633.54 ⁺ (748.50)	115.67 (314.32)	<0.001	103	798.78 ⁺ (923.26)	77.38 (58.18)	<0.001
Annual exacerbations, mean (SD)	171	4.60 (3.49)	1.24 (1.61) ^{*f}	<0.001	147	4.33 (3.55)	0.73 (1.14) ^{*f}	<0.001
Prednisolone dose, mean (SD), mg/day	49	14.31 (9.86) ⁺ -	5.49 (7.47) 21/49 (42.9%)	0.002	41	9.48 (9.56) ⁺ -	4.14 (6.12) 22/41 (53.7%)	<0.001
Patients with prednisone 0 mg/day, n/n (%)								
ACT score, mean (SD)	139	13.57 (4.90)	20.60 (3.98)	<0.001	121	14.63 (5.16)	21.09 (3.72)	<0.001
Patients with ACTscore >20, %		12.1%	69.8%			18.5 %	76.0 %	
Pre-BD FEV1, mean (SD), L	117	1.80 (0.72)	1.99 (0.64)	<0.001	94	1.99 (0.81)	2.19 (0.87)	<0.001
Pre-BD FEV1, mean (SD), %	114	69.66% (23.05)	79.93% (22.04)	<0.001	95	70.67% (21.25)	81.30% (21.15)	<0.001
Pre-BD FEV1 z-score, mean (SD)	117	-2.11 (1.56)	-1.61 (1.49)	<0.001	94	-2.04 (1.42)	-1.54 (1.39)	<0.001

*p<0.05 for intergroup difference at baseline
⁺p<0.05 for intergroup difference at 12 months
^fp<0.05 for intergroup difference of change