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Peter Howarth, MBBS, DM, FRCP, Geoffrey Chupp, MD, Linda M. Nelsen, MHS, Eric S. Bradford, MD, Daniel J. Bratton, PhD, Steven G. Smith, PhD, Frank C. Albers, MD, PhD, Guy Brusselle, MD, PhD, FERS, Claus Bachert, MD, PhD

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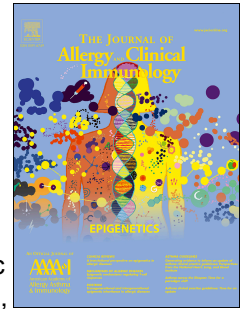
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Severe eosinophilic asthma with nasal polyposis: A phenotype for improved sino-nasal and asthma outcomes with mepolizumab therapy

Peter Howarth MBBS, DM, FRCP,¹ Geoffrey Chupp MD,² Linda M Nelsen MHS,³ Eric S Bradford MD,⁴ Daniel J Bratton PhD,⁵ Steven G Smith PhD,⁴ Frank C Albers MD, PhD,^{6*} Guy Brusselle MD, PhD, FERS,⁷ Claus Bachert MD, PhD⁸

¹Global Medical Franchise, GSK House, Brentford, Middlesex, UK; ²Yale Center for Asthma and Airways Disease (YCAAD), Yale School of Medicine, New Haven, CT, USA; ³Value Evidence and Outcomes, GSK, Collegeville, PA, USA; ⁴Respiratory Therapeutic Area, GSK, Research Triangle Park, NC, USA; ⁵Clinical Statistics, GSK, Stockley Park, Uxbridge, Middlesex, UK; ⁶Respiratory Medical Franchise, GSK, Research Triangle Park, NC, USA; ⁷Department of Respiratory Medicine, University Hospital Ghent, C. Heymanslaan 10, 9000 Ghent, Belgium; ⁸Upper Airways Research Laboratory, University Hospital Ghent, C. Heymanslaan 10, 9000 Ghent, Belgium

*Affiliation at time of study, currently employed by Avillion US, Inc., IL, USA

Corresponding author:

Name: Professor Peter Howarth

Address: Global Medical Franchise, GSK House, Great West Road, Brentford, Middlesex, UK

Tel: +447341079702

Email: peter.h.howarth@gsk.com

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Conflicts of Interests

GC has served on advisory boards and speakers bureaus for AstraZeneca, Genentech, Boehringer Ingelheim, Teva, Regeneron, Circassia, and GSK, and received research grants from AstraZeneca and institutional grants from AstraZeneca, Genentech, Boehringer Ingelheim, and GSK. CB serves on the advisory boards of ActoBiotics, ALK, ASIT Biotech, AstraZeneca, Novartis, Sanofi, and Stallergenes. GB reports honoraria for lectures from AstraZeneca, Boehringer Ingelheim, Chiesi, GSK, Novartis, Pfizer, Teva, and Zambon; he is a member of advisory boards for AstraZeneca, Boehringer Ingelheim, GSK, Novartis, Sanofi/Regeneron, and Teva. PH, LN, EB, DJB, and SGS are employees of GSK and own stocks/shares in GSK. FA is a former employee of GSK and holds GSK stocks/shares and is currently employed by Avillion US, Inc.

Data sharing statement: Anonymized individual participant data from the parent studies listed within this publication and their associated documents can be requested for further research from www.clinicalstudydatarequest.com.

Capsule Summary: While mepolizumab improves health-related quality of life and reduces exacerbation frequency in patients with severe eosinophilic asthma (SEA), those with SEA and nasal polyposis have a clinical phenotype that exhibits enhanced benefit with mepolizumab treatment.

Key words: Mepolizumab, eosinophil, interleukin-5, asthma, nasal polyps, exacerbation

TO THE EDITOR:

Nasal polyposis (NP) is a chronic inflammatory disease of the sinuses that can cause severe nasal symptoms and systemic symptoms that include fatigue, difficulty sleeping, and impairments in social, emotional, and lifestyle well-being.¹ Patients with severe eosinophilic asthma (SEA) frequently have comorbid NP, which may impact asthma severity.¹ The anti-interleukin(IL)-5 monoclonal antibody mepolizumab improves health-related quality of life (HRQoL) and exacerbation rates in patients with SEA;^{2,3} however, its effect on HRQoL based on the presence of NP has not been examined. This letter describes results from a post hoc analysis of the MUSCA study² (n=551; GSK ID: 200862/NCT02281318) and a meta-analysis (GSK ID: 208115) of MUSCA and MENSA³ (n=576; GSK ID: 115588/NCT01691521); their combined objective was to determine the change in HRQoL in mepolizumab-treated patients with SEA either with or without NP.

MENSA and MUSCA were Phase III, placebo-controlled, randomized, double-blind, parallel-group, multicenter studies. Full study details have been published.^{2,3} Briefly, patients ≥ 12 years of age with SEA (defined as asthma requiring regular treatment with high-dose inhaled corticosteroids and additional controller medication,⁴ plus a blood eosinophil count ≥ 150 cells/ μ L at screening or ≥ 300 cells/ μ L in the prior year) and a history of ≥ 2 exacerbations requiring systemic corticosteroids in the year preceding enrollment received standard care plus mepolizumab 100 mg subcutaneously, or placebo, every 4 weeks for 32 (MENSA) or 24 (MUSCA) weeks.

In both studies, the presence of NP was determined from patients' medical records and/or external nasal examination at baseline. MUSCA assessed the mean change from baseline in SinoNasal Outcomes Test (SNOT-22) score at the end of treatment (Week 24); we analyzed this post hoc using mixed model repeated measures. The SNOT-22 is a 22-item patient-reported outcome tool developed for use in patients with chronic rhinosinusitis (CRS) with and without NP, assessing upper airways/nasal symptoms and HRQoL impacts of CRS; the established minimally clinically important difference (MCID) representing an improvement is an 8.9-point decrease.⁵ A shared outcome of both studies was the mean change from baseline in the annual rate of clinically significant exacerbations (asthma worsening requiring systemic corticosteroids and/or hospitalization, and/or an emergency room visit). Annualized exacerbation rates were analyzed using a negative binomial regression model and treatment differences for each study were combined using an inverse variance weighted fixed-effects meta-analysis.

For the MUSCA post hoc analysis, of 551 patients included in the modified intent-to-treat population, 105 (19%) had NP at baseline. Overall, 422 patients completed the SNOT-22 questionnaire at baseline (and were therefore included); 80 (19%) had NP. Mean (SD) baseline SNOT-22 scores were 43.6 (22.3) and 31.1 (20.2) for patients with and without NP. This is consistent with the reported SNOT-22 scores of patients undergoing surgery for NP and/or CRS,⁵ indicating greater disease burden among patients with versus without NP. Among patients with NP, mepolizumab and placebo reduced the mean (standard error) SNOT-22 score by -13.7 (2.6) and -1.9 (3.0) from baseline to Week 24. The treatment difference of -11.8 (95% confidence interval [CI]: -19.8, -3.9) (**Figure 1**) exceeded the MCID, indicating a clinically meaningful improvement.⁵ In patients with SEA without NP the impact of mepolizumab was less, with a treatment difference of -4.9 (95% CI: -8.3, -1.6). However, improvements in HRQoL related to lower airway symptoms (as measured by the SGRQ [St George's respiratory questionnaire] score) with mepolizumab were evident in both groups, with treatment differences (95% CI) of -14.6 (-21.4, -7.7) and -6.5 (-9.6, -3.5) in those with and without NP; these both exceeded the MCID of 4.0. This shows that mepolizumab has greater benefit in the upper and lower airways in patients with NP and SEA versus SEA alone.

For the meta-analysis of MENSA/MUSCA, of 936 patients included, 166 (18%) had NP at screening. Patients with NP had higher baseline geometric mean (SD log) eosinophil counts than those without NP (440 [0.938] vs 290 [1.010] cells/ μ L). Mean (SD) baseline annual exacerbation rates were 3.1 (2.1) and 3.2 (2.3) for patients with and without NP. Mepolizumab versus placebo reduced the annual rate of clinically significant exacerbations in patients with SEA regardless of NP status, but to a greater extent in patients with NP (80%) than without NP (49%) (**Figure 2**).

Overall, our results suggest that patients with SEA and comorbid NP have a higher disease burden, as reflected by the SNOT-22 and SGRQ scores, and greater systemic eosinophilic inflammation than those with SEA but no diagnosis of NP. Furthermore, in support of other studies of biologics in SEA,^{6,7} clinical improvements with mepolizumab were greater in patients with SEA and NP than those without NP. It should be noted that in this analysis NP was identified based on the patients' medical records and/or external nasal examination, which may not be as reliable as performing one standardized physical examination. Nonetheless, these data suggest that patients with the clinical phenotype of SEA plus NP may have an even greater response to treatment with mepolizumab due to their morbidity. Consistent with this it is known that mepolizumab, as a systemic therapy, impacts on the upper airways, with improvement in NP size and HRQoL in patients with NP.⁸ The local

generation of IL-5 within the upper and lower airways in patients with SEA with NP may explain the higher circulating blood eosinophil levels compared with patients with SEA without NP.⁹ As higher blood eosinophil counts are a predictive biomarker of better response to mepolizumab in SEA,^{2,3} it may not be surprising that mepolizumab has greater benefit in reducing severe exacerbations in patients with SEA plus NP. However, it is important to demonstrate that this phenotype is associated with an enhanced response to mepolizumab in the clinical setting.

In conclusion, although patients with SEA demonstrated improvements in HRQoL and exacerbations with mepolizumab treatment regardless of the presence of NP, patients with SEA and concomitant NP have a phenotype that demonstrates greater benefit with mepolizumab therapy compared with patients with SEA in the absence of NP. These results suggest that mepolizumab may directly affect upper airway type 2 inflammatory conditions, with prospective studies required to demonstrate this further.

Peter Howarth MBBS, DM, FRCP (GSK, Brentford, Middlesex, UK)

Geoffrey Chupp MD (Yale School of Medicine, New Haven, CT, USA)

Linda M Nelsen MHS (GSK, Collegeville, PA, USA)

Eric S Bradford MD (GSK, Research Triangle Park, NC, USA)

Daniel J Bratton PhD (GSK, Stockley Park, Uxbridge, Middlesex, UK)

Steven G Smith PhD (GSK, Research Triangle Park, NC, USA)

Frank C Albers, MD, PhD (GSK, Research Triangle Park, NC, USA; Avillion US, Inc., IL, USA)

Guy Brusselle MD, PhD, FERS (University Hospital Ghent, C. Heymanslaan 10, 9000 Ghent, Belgium)

Claus Bachert MD, PhD (University Hospital Ghent, C. Heymanslaan 10, 9000 Ghent, Belgium)

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Figure 1. Change from baseline in SNOT-22 score* at Week 24 in MUSCA patients with SEA with or without NP.

*Analyzed using mixed model repeated measures adjusted for baseline value, number of exacerbations in the year prior to the study, baseline maintenance oral corticosteroid therapy, region and baseline % predicted pre-bronchodilator FEV₁. The dashed line as positioned represents the established MCID (from baseline) for SNOT-22 (-8.9 points). CI, confidence interval; FEV₁, forced expiratory volume in 1 second; LS, least squares; MCID, minimally clinically important difference; NP, nasal polyps; SEA, severe eosinophilic asthma; SNOT-22, SinoNasal Outcomes Test-22

Figure 2. Rate ratio of on-treatment annual clinically significant exacerbations* by presence of NP in patients with SEA who took part in the MENSA and MUSCA studies.

*Analyzed using a negative binomial regression model adjusted for treatment group, baseline maintenance oral corticosteroid therapy, region, number of exacerbations in the year prior to the study and baseline % predicted pre-bronchodilator FEV₁; [†] annualized rates were calculated from the full treatment period of each study (32 weeks for MENSA, 24 weeks for MUSCA). CI, confidence interval; FEV₁, forced expiratory volume in 1 second; NP, nasal polyps; SEA, severe eosinophilic asthma

