No Genetic Associations Were Identified with Mepolizumab Efficacy in Eosinophilic COPD

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Background

- Monoclonal antibodies targeting interleukin-5 (IL-5) are effective for the treatment of eosinophilic diseases.
- Although these agents, such as mepolizumab, are approved for the treatment of eosinophilic indications (e.g., severe asthma and eosinophilic granulomatosis with polyangiitis) and are under investigation for other eosinophilic indications (e.g., COPD, nasal polyps, hypereosinophilic syndrome), not all patients receive benefit.
- In COPD, response to mepolizumab was less than seen in patients with severe asthma.
- Therefore, identification of genetic predictors of response to mepolizumab in COPD may be important in the future development and use of mepolizumab.

Objective

- The aim of this post-hoc, exploratory pharmacogenetic study was to determine if genetic variants are associated with treatment response to mepolizumab added to standard of care in subjects with eosinophilic COPD.

Methods

- Study Designs and Treatment
  - 680 subjects with COPD and elevated eosinophil levels (≥150 cells/µl at screening or ≥300 cells/µl in the 12 months prior to study) who were treated with mepolizumab in addition to standard of care were in the intent to treat (ITT) sample from 2 phase III studies (METREX (NCT02105948) and METREO (NCT02105961)) assessing efficacy and safety of mepolizumab (**Table 1**).
  - 610 of these 680 subjects provided written informed consent for genetic analysis and were tested for genetic effects on mepolizumab efficacy.

Table 1. Studies Included

Study Title	Study Acronym and IDs	Estimated Mean Annual Rate (95% CI) of Moderate and/or Severe Exacerbation in Mepolizumab-treatment Group	PGx Sample Collection Rate per Study
Mepolizumab vs. Placebo as add-on treatment for frequently exacerbating COPD patients	METREX (MEA117106, NCT02105948)	1.40 (1.23, 1.60) (100mg mepolizumab)	88%
Mepolizumab vs. Placebo as add-on treatment for frequently exacerbating COPD patients characterized by eosinophil level	METREO (MEA117113, NCT02105961)	1.19 (1.02, 1.38) (group receiving 100mg mepolizumab) 1.27 (1.09, 1.48) (group receiving 300 mg mepolizumab)	91%

PGx, Pharmacogenetics

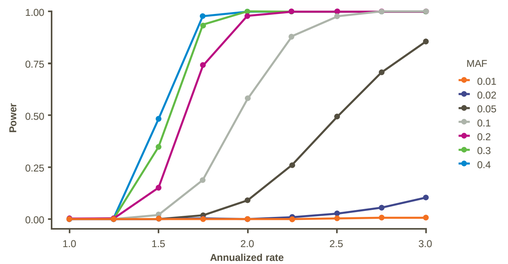
- Endpoints included:
  - Exacerbation Endpoints
    1. Primary Endpoint: frequency of moderate and/or severe COPD exacerbations per year.
    2. Secondary Endpoint: frequency of COPD exacerbations requiring hospitalization or emergency department visit per year.
  - Quality of Life Exploratory Endpoints
    - QoL Endpoint 1: change from baseline mean total St. George's Respiratory Questionnaire (SGRQ) score (week 24) adjusted for baseline disease severity (% predicted post-bronchodilator FEV_1).
    - QoL Endpoint 2: SGRQ response defined by achieving a 4 unit or greater decrease of SGRQ score from baseline (week 24).
  - Genotyping:
    - Affymetrix Axiom Biobank Genotyping Array with GSK custom content v2
    - ~49 million variants were imputed using the 1000G phase 3 project reference panel.

- Genome-wide association analysis:
  - Genetic variants with a minor allele frequency (MAF) ≥1% and imputation quality score r^2≥0.30 were analyzed using additive models.
  - A generalized linear model with negative binomial link function was used to test the association of genetic markers with Exacerbation Endpoints with Log_e (time in study) as an offset variable.
    - Covariates included study number, smoking status (current vs. never/ex-smoker), exacerbation number in previous year (≤2, 3, ≥4), baseline disease severity (% predicted post-bronchodilator FEV1), geographic region, mepolizumab dosage (100 or 300 mg), blood eosinophil group level (screening visit count: <150 cells/µl, 150 - <300 cells/µl, 300 - <500 cells/µl, ≥500 cells/µl), and five genome-wide principal components (PCs) to capture population structure.
  - A linear regression model with log_e (time in study) as an offset variable was used to test genetic effects on change from baseline mean total SGRQ score, adjusted for disease severity) using inverse quantile normalized residuals.
  - Logistic regression was used to test for genetic effects on binary SGRQ response.
    - Covariates for both SGRQ analyses included study, smoking status, geographic region, mepolizumab dosage, blood eosinophil group level at screening and 5 PCs.
  - For all analyses, a type 1 error rate of 0.05 was used with the test statistic adjusted for genomic control and number of genetic variants tested. The significance threshold for genome-wide variants was $p \leq 5 \times 10^{-8}$.

Results

- Demographic and endpoint characteristics were similar across ITT and PGx Genetics Analysis Populations (GAP) (**Table 2**).
- With 610 subjects in the GAP for the Exacerbation Endpoint analyses, detection power reached 80% when the annualized rate of moderate/severe exacerbation exceeds 1.85 with a minor allele frequency (MAF>0.2) (**Figure 1**).
- No genetic variant was significantly associated with frequency of exacerbation or with change from baseline SGRQ score (**Figure 2A** and **B**). Similarly, no variants were associated with frequency of COPD exacerbations requiring hospitalization or emergency department visit or with binary SGRQ response (data not shown).

Figure 1. Power to detect genetic effects, by variants, on Frequency, using moderate and/or severe COPD Exacerbations in Genetics Analysis Population



MAF, minor allele frequency.

Table 2. Demographic and endpoint characteristics of ITT and Genetic Analysis Population

Characteristic	ITT	Genetics Analysis Population
Total N	680	610
Treatment, n (%)		
Mepolizumab, 100 mg SC	455 (67%)	400 (66%)
Mepolizumab, 300 mg SC	225 (33%)	210 (34%)
Sex, n (%)		
Female	242 (36%)	222 (36%)
Male	438 (64%)	388 (64%)
Age, Years, Mean (SD)	64.93 (8.79)	64.69 (8.94)
Smoking history, n (%)		
Current	188 (28%)	167 (27%)
Never/Former	492 (72%)	443 (73%)
FEV_1 post-bronchodilator percent predicted at baseline, Mean (SD)	45.72 (15.25)	45.63 (15.50)
Eosinophil Group at screening in cells/µl, n (%)		
<150	98 (14%)	85 (14%)
150 - <300	331 (9%)	295 (8%)
300 - <500	162 (24%)	146 (24%)
≥500	87 (13%)	82 (13%)
Missing	2 (<1%)	2 (<1%)
Exacerbation history in previous year, n (%)		
≤2	433 (64%)	386 (63%)
3	129 (19%)	114 (19%)
≥4	118 (17%)	110 (18%)
Race, n (%)		
White	559 (82%)	504 (83%)
Asian	83 (12%)	73 (12%)
American Indian or Alaskan Native	19 (3%)	18 (3%)
Black or African American	8 (1%)	5 (1%)
Multiple	11 (2%)	10 (2%)
Ethnicity, n (%)		
Hispanic or Latino	111 (16%)	108 (18%)
Not Hispanic or Latino	569 (84%)	502 (82%)
Exacerbation		
Exacerbation frequency: Count, n (%)		
0	274 (40%)	248 (41%)
1	157 (23%)	134 (22%)
2	117 (17%)	104 (17%)
3	64 (9%)	59 (10%)
4	31 (5%)	29 (5%)
5	22 (3%)	21 (3%)
≥6	15 (2%)	15 (2%)
Exacerbation requiring hospitalization or emergency department visit: Count, n (%)		
0	563 (83%)	500 (82%)
1	74 (11%)	71 (12%)
2	29 (4%)	25 (4%)
3	9 (1%)	9 (1%)
4	2 (0.3%)	2 (0.3%)
5	2 (0.3%)	2 (0.3%)
6	1 (0.1%)	1 (0.2%)
SGRQ		
SGRQ Change from baseline for week 24, Mean (SD), n	-5.52 (16.00), 611	-5.61 (16.00), 555
SGRQ response week 24, n (%)		
Responders	307 (50%)	280 (50%)

FEV_1, Forced expiratory volume in one second; SC, subcutaneous; SD, Standard Deviation; SGRQ, St. George's Respiratory Questionnaire

Figure 2A. No genetic variant associates with frequency of moderate and/or severe COPD exacerbation (weeks 0-52) at the GWAS level ($p \leq 5 \times 10^{-8}$)

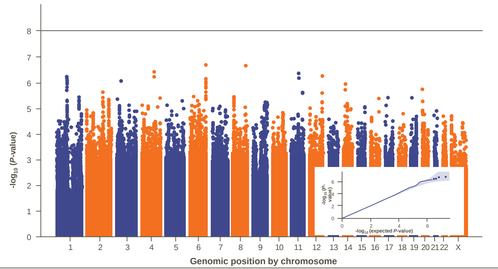
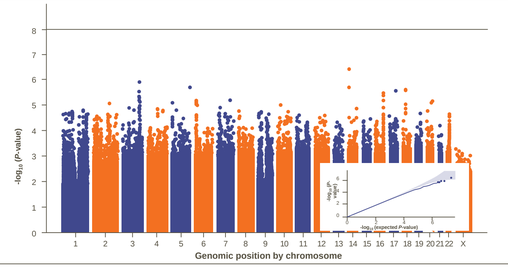


Figure 2B. No genetic variant associates with the Quality of Life endpoints, change from baseline mean total SGRQ score (at the GWAS level, $p \leq 5 \times 10^{-8}$)



Conclusions

- This post-hoc PGx study had statistical power to detect large genetic effects.
- No genetic effects on mepolizumab-treatment response were identified in this analysis of patients with eosinophilic COPD from two large phase III studies.
- Therefore, common genetic variants are unlikely to exert large clinical effects on mepolizumab treatment response in patients with eosinophilic COPD.

References

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