No Genetic Associations Were Identified with Mepolizumab Efficacy in Eosinophilic COPD

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Background
- Microbiological antibodies targeting interleukin-5 (IL-5) are effective for the treatment of eosinophilic diseases.
- Although these targets such as mepolizumab are approved for the treatment of eosinophilic diseases, study endpoints are broad and lack granularity.
- We aimed to study genetic variants in COPD patients with eosinophilia to identify targets and markers that may improve clinical endpoints.

Objective
- To identify genetic variants associated with mepolizumab efficacy in eosinophilic COPD.

Methods
- **Study Design and Treatment**: 655 subjects with COPD and elevated eosinophil counts (≥100 cells/μL) at screening or ≥200 cells/μL in the 12 months prior to study were treated with mepolizumab in addition to standard care. The primary outcome was the change from baseline to week 16 in the total SGRQ score.
- **Covariates**: Patients with a history of asthma were excluded.
- **Genetic Analysis**: Genomic DNA was isolated from peripheral blood samples. Genetic variants in the coding or non-coding regions of genes were analyzed using the 1000 Genomes Project.
- **Statistical Analysis**: The association between genetic variants and efficacy was assessed using linear regression models.

Results
- **Endpoints**:
  - Exacerbation Endpoints: 1. Primary Endpoint: Frequency of moderate and/or severe COPD exacerbations per year.
  - Secondary Endpoint: Frequency of COPD exacerbations requiring hospitalization or emergency department visit.
  - Quality of Life Exemplary Endpoints: 1. QoL: Exemplar 1: Change from baseline mean total St. George’s Respiratory Questionnaire (SGRQ) score (week 48).
  - Genotypic: Allelic and Genotypic associations were assessed using the chi-square test (week 48).
- **Genetic Analysis**: Genomic DNA was extracted from peripheral blood samples. Genetic variants in the coding or non-coding regions of genes were analyzed using the 1000 Genomes Project.
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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 the large phase III studies.**
- **Therefore, common genetic variants are unlikely to have large clinical effects on mepolizumab treatment response in patients with eosinophilic COPD.**

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References

**Figure 1**: Power to detect genetic effects, by variant, on frequency, using moderate dose eosinophilic COPD exacerbation as the primary endpoint.

**Table 1**: Genotypic and Exemplar characteristics of ITT and ITT Analysis Population.

**Table 2**: Geographical and exemplar characteristics of ITT and ITT Analysis Population.

**Table 3**: Genotypic and Exemplar characteristics of ITT and ITT Analysis Population.

**Figure 2A**: The genetic variants associated with frequency of moderate and/or severe COPD exacerbations at baseline and visit 41.

**Figure 2B**: The genetic variants associated with frequency of moderate and/or severe COPD exacerbations at baseline and visit 41.

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