Genetic Variants Do Not Predict Acute COPD Exacerbations or Treatment Response to Fluticasone Furoate/Umeclidinium/Vilanterol and Its Components

Poster No. P1591

Introduction

• Combination treatments, targeting multiple disease processes, benefit subjects with acute exacerbation of chronic obstructive pulmonary disease (AECOPD). However, predicting treatment response and exacerbation risk remain challenging and few studies have investigated the genetic basis of AECOPD risk and treatment efficacy. To address this gap, we investigated genetic associations with AECOPD disease and response to combination treatment with Fluticasone Furoate/Umeclidinium/Vilanterol (FF/UMEC/VI) and its individual components (FF, UMEC, VI) in COPDGene and ECLIPSE studies.

Methods

• The genetic basis of AECOPD risk was investigated in 19,161 subjects of white European ancestry from 23 clinical trials and 2 disease cohorts (Table 1A). Exacerbator history data from the prior 12 months was used to define AECOPD frequency or risk. As CTT116855 enrolled only patients who experienced one or more exacerbations in the prior 12 months, AECOPD frequency was defined using 52-week on-treatment data, analyzed without respect to treatment, and then meta-analyzed.

• AECOPD pharmacogenetic (PGx) effects were examined in 8,439 moderate to severe COPD patients in CTT116855 (Table 1B) with exacerbation rate, long-term function and quality of life endpoints. Analyses were conducted for treatment arms (FF/UMEC/VI, FF/VI and FF/UMEC) and by molecule (FF/UMEC/VI, FF and VI). The AECOPD frequency stratum 52-week on-treatment arms combined.

• PGx endpoints:
  - Annual rate of on-treatment moderate/severe exacerbations. Moderate exacerbation was defined as hospitalization.
  - Annual rate of on-treatment moderate/severe exacerbations in subjects with eosinophils ≥150 cells/μl at baseline.
  - Change from baseline at Week 4 in trough forced expiratory volume in one second (FEV1).
  - Change from baseline at Week 28 in St George’s Respiratory Questionnaire (SGRQ).

• Progression of subjects with Week 24 with a composite clinically important deterioration (CID) including SGRQ score.

• PGx results were followed-up in 2,201 subjects drawn from 3 of the 23 clinical trials that had data on 52-week exacerbation rates (Table 1B).

Statistical models

• Generalized linear regression with the negative binomial link function and log (observation time or time on treatment), as an offset was used to model exacerbation frequency and exacerbation rate.

• Logistic regression was used to model binary endpoints (exacerbations vs no-exacerbations: subjects on CD or non-CID).

• Linear regression was used to model change from baseline endpoints.

• All models included 10 genetic principal components (PGCs) and endpoint specific covariates, as in all models, additive genetic effects were tested for each variant.

Genetics data

• ~10 million genome-wide variants were included in the AECOPD disease and PGx analyses genome-wide association analyses (GWAS). A small number of candidate variants (n=23) were evaluated in the PGx analysis. Multiple testing correction for the number of genetic variants, but not for multiple analyses by molecule.

Results

Subject description

• Subjects were predominantly male and over 40 years of age. COPD severity ranged from moderate to very severe.

• Table 1A. Characteristics of AECOPD PGx analyses.

Table 1a. Characteristics of subjects in AECOPD disease analyses

| Study/O | Clinical arm | Investigator/Institution | Subjects enrolled | % complete | FEV1 (FVC) | Annual exacerbation rate | Annual exacerbation rate * eosinophils >_150 | Baseline | Change from baseline at Week 4 | Change from baseline at Week 28 in SGRQ | Monthly | Monthly
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<td>FF/UMEC/VI</td>
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<td>10,355</td>
<td>100%</td>
<td>45.3 (14.5)</td>
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Analysis results

• AECOPD disease risk: we did not identify significant associations despite being well powered to detect modest effects.

• AECOPD PGx analysis: none of the candidate variants were associated with any endpoint in any arm or molecule. One GWAS variant reached statistical significance (p=1.8x10^-8). As the minor allele, T, with a frequency of 10%, was associated with an increased exacerbation rate and per minor allele annual increase (OR=2.0; 95% CI 1.1-3.5) (Figure 1).

• PGx results were followed-up in 2,201 subjects drawn from 3 of the 23 clinical trials that had data on 52-week exacerbation rates (Table 1B).

• Figure 2. Mild to severe exacerbation rate in subjects with eosinophils ≥150 cells/μl treated with FF/UMEC/VI.

Table 1B. Characteristics of AECOPD PGx populations

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<th>Investigator/Institution</th>
<th>Subjects enrolled</th>
<th>% complete</th>
<th>FEV1 (FVC)</th>
<th>Annual exacerbation rate</th>
<th>Annual exacerbation rate * eosinophils &gt;_150</th>
<th>Baseline</th>
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Conclusions

• Common genetic variants play limited roles in AECOPD disease and are unlikely to robustly predict responses to triple therapy or its components in moderate to severe COPD.

• Even if recognized, the MKKS AECOPD PGx signal is unlikely to be of clinical utility in relation to therapy and it is more likely we have identified a small subpopulation that do not respond well to any of the combination treatments.

Acknowledgments

• We thank the subjects and investigators who participated in the clinical trials and cohort studies, without which this research would not have been possible. We thank Sandy Stinnett, Todd Johnson, Matt Nelson, Sally Lettis, Sally Kilbride, Ralf van der Valk and Chris Compton for their support, advice and collaboration.

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