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

Poster No. P1501

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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 (FF, an inhaled corticosteroid), umeclidinium (UMEC, a long-acting muscarinic antagonist), and vilanterol (VI, an ultra-long-acting β_2 adrenoreceptor agonist) and for each component.

Methods

- The genetic basis of **AECOPD risk** was investigated in 19,841 subjects of white European ancestry from 23 clinical studies and 2 disease cohorts (**Table 1A**). Exacerbation 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, lung function and quality of life endpoints. Analyses were conducted by treatment arm (FF/UMEC/VI, FF/VI, UMEC/VI) and by molecule (FF=FF/UMEC/VI + FF/VI; UMEC=FF/UMEC/VI + UMEC/VI; VI=all three treatment arms combined).
- **PGx endpoints:**
  - Annual rate of on-treatment moderate/severe exacerbations. Moderate: antibiotics/oral steroids. Severe: 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 (FEV_1).
  - Change from baseline at Week 28 in St George's Respiratory Questionnaire (SGRQ).
  - Proportion of subjects at 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 studies 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 (exacerbators vs non-exacerbators; subjects with CID vs non-CID).
- Linear regression was used to model change from baseline endpoints.
- All models included 10 genetic principal components (PCs) and endpoint specific covariates. 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 corrected for the number of genetic variants, but not for multiple analyses by endpoint, treatment or subgroup. The significance thresholds applied were $P \leq 5E\text{-}8$ for the AECOPD disease GWAS, $P \leq 2.5E\text{-}8$ for the AECOPD PGx GWAS, and $P \leq 0.001$ for the AECOPD PGx candidate variant analysis.

Results

Subject description

- Subjects were predominantly male and over 40 years of age. COPD severity ranged from moderate to very severe.
- The AECOPD PGx Main and Follow-up populations are similar with respect to age, sex, race, smoking history, lung function and baseline eosinophils. CTT116855 had a more severe exacerbation history than the follow-up studies.

Table 1A. Characteristics of studies in AECOPD disease analysis

Study ID	Clinical phase	Intent-to-treat subjects, N	Subjects in genetic analysis, N	Sex, % female	FEVPPSC, mean (SD)	Smoking history, % current smokers	COPD severity	Study duration, weeks
CTT116855	IIIA	10,355	5779	41%	45.3 (14.5)	40%	Moderate to very severe	52
CTT116853	IIIA	1811	1009	26%	45.5 (13.4)	46%	Moderate to very severe	24
HZC102970	IIIA	1636	1064	45%	45.6 (13.3)	47%	Moderate to severe	52
HZC102871	IIIA	1627	927	44%	45.2 (13.4)	47%	Moderate to severe	52
200820	IIIA	1621	513	30%	50.0 (10.4)	52%	Moderate to very severe	12
200812	IIIB	1057	394	26%	46.2 (13.9)	44%	Moderate to very severe	24
201315	IV	1036	410	33%	51.1 (10.3)	52%	Moderate to severe	12
201316	IIIB	1017	440	28%	51.8 (10.0)	52%	Moderate to severe	12
200109	IIIB	619	128	23%	48.0 (12.5)	48%	Moderate to very severe	12
200110	IIIB	620	250	40%	46.8 (12.0)	61%	Moderate to very severe	12
DB2116961	IIIB	967	360	26%	48.2 (12.2)	46%	Moderate to very severe	12
DB2113373	IIIA	1538	809	31%	47.3 (13.1)	51%	Moderate to very severe	24
DB2113361	IIIA	1493	939	37%	48.7 (12.3)	54%	Moderate to very severe	24
DB2113374	IIIA	872	360	37%	45.6 (13.7)	46%	Moderate to very severe	24
DB2113360	IIIA	846	460	30%	47.9 (12.8)	55%	Moderate to very severe	24
DB2113359	IIIA	563	334	31%	55.5 (12.1)	61%	Moderate to severe	52
AC4113589	IIB	285	187	44%	53.2 (9.2)	60%	Moderate	4
AC4115408	IIIA	206	113	39%	47.5 (13.5)	50%	Moderate to very severe	12
B2C111045	IIB	606	305	41%	48.5 (11.6)	57%	Moderate	4
HZC113108	IIIB	446	115	30%	48.8 (14.0)	47%	Moderate to very severe	24
HZC112206	IIIA	1031	298	38%	48.4 (12.2)	64%	Moderate to very severe	24
HZC113107	IIIB	528	246	19%	49.6 (11.0)	45%	Moderate to very severe	12
HZC112207	IIIA	1226	657	26%	47.5 (12.4)	52%	Moderate to very severe	24
ECLIPSE	Disease	NA	1434	31%	43.8 (14.8)	36%	Moderate to very severe	156
COPDGene	Disease	NA	2310	42%	50.1 (18.1)	36%	Moderate to very severe	Up to 4 years

FEVPPSC = Percent predicted FEV$_1$ post-bronchodilator at baseline.

Table 1B. Characteristics of AECOPD PGx populations

Study	Subject number	Treatment arms (µg), N	Sex, % female	Age, years mean (SD)	White European, %	FEVPPSC, mean (SD)	Smoking history, % current smokers	Exacerbation history, % ≥2 moderate or ≥1 severe	Baseline eosinophils, % ≥150 cells/µl
PGx main study									
CTT116855	8439	FF/UMEC/VI (100/62.5/25): 3378 FF/VI (100/25): 3366 UMEC/VI (62.5/25): 1695	37%	65.2 (8.32)	83%	45.8 (14.81)	36%	71%	57%
PGx follow-up studies									
CTT116853 52-week extension	185	FF/UMEC/VI (100/62.5/25): 185	24%	63.9 (7.70)	100%	47.0 (13.63)	43%	55%	62%
HZC102871	996	FF/VI (100/25): 327 FF/VI (200/25): 345 VI (25): 324	41%	63.9 (9.18)	81%	44.9 (13.29)	42%	42%	64%
HZC102970	1020	FF/VI (100/25): 331 FF/VI (200/25): 345 VI (25): 344	45%	64.0 (9.03)	88%	45.9 (13.31)	45%	46%	62%

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 was associated with any endpoint in any arm or molecule. One GWAS variant reached significance (P=1.8E-10). rs56195836 (*MAPK8*) was associated with moderate to severe exacerbation rate in subjects on FF with baseline blood eosinophils ≥150 cells/µl. The minor allele, T, with a frequency of 10%, was associated with an increased exacerbation rate with a per minor allele annual rate increase (SE) of 0.28 (0.05) (**Figure 1**).

Figure 1. Moderate to severe exacerbation rate in subjects with baseline eosinophils ≥150 cells/µl treated with FF

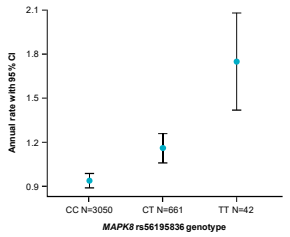
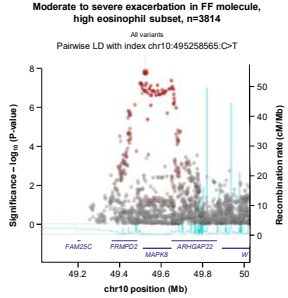


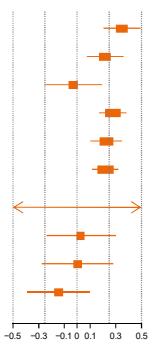
Figure 2. *MAPK8* region plot



- Several variants in the *MAPK8* genomic region are highly correlated (increased red indicates increased correlation) with rs56195836 (largest symbol) as can be seen in **Figure 2**. None of these variants are predicted to be functional and none are eQTLs for *MAPK8* expression.
- The same effect direction was observed in the two FF containing treatment arms, FF/UMEC/VI and FF/VI, but not in the non-FF containing UMEC/VI arm in CTT116855 (**Figure 3**). We next examined the effect of rs56195836 in the 3 follow-up studies and saw no effect in the treatment arms or by molecule.

Figure 3. Forest plot of the *MAPK8* effect in subjects with baseline eosinophils ≥150 cells/µl across arms & molecules in CTT116855 and three follow-up studies

Study	Treatment	N	Rate difference (95% CI)	P-value
CTT116855	FF/UMEC/VI	1885	0.35 (0.21, 0.49)	2.61E-6
CTT116855	FF/VI	1925	0.22 (0.08, 0.36)	0.0008
CTT116855	UMEC/VI	971	−0.03 (−0.25, 0.19)	0.80
CTT116855	FF	3810	0.28 (0.18, 0.38)	1.81E-8
CTT116855	UMEC	2856	0.23 (0.11, 0.35)	0.0002
CTT116855	VI	4781	0.22 (0.12, 0.32)	1.52E-6
Follow-up	FF/UMEC/VI	108	−0.69 (−2.24, 0.86)	0.38
Follow-up	FF/VI	818	0.03 (−0.24, 0.30)	0.81
Follow-up	FF	926	0.004 (−0.27, 0.28)	0.97
Follow-up	VI	1324	−0.14 (−0.38, 0.10)	0.23



Conclusions

- Common genetic variants play limited roles in AECOPD disease and are unlikely to robustly predict response to triple therapy or its components in moderate to severe COPD.
- Even if replicated, the *MAPK8* 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 analyzed therapies.

Disclosures

- This study was funded by GSK. LH, AY, JH, MC, SG, DL, NM and CC are employees of GSK. DF, LC and PSJ are employees of Parexel and under contract with GSK. The COPDGene study was supported by NIH grants U01HL089856 and U01HL089897 and by the COPD Foundation through contributions made by an Industry Advisory Board comprised of Pfizer, AstraZeneca, Boehringer Ingelheim, Novartis and Sunovion.
- On behalf of all authors, an audio recording of this poster was prepared by Pamela St Jean, who did not receive any payment for this recording.

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, Toby Johnson, Matt Nelson, Sally Lettis, Sally Kilbride, Ralf van der Valk and Chris Compton for their support, advice and consultation.

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Prepared for the American College of Chest Physicians Congress (2020)