Relation of FEV_1 to COPD Patient Outcomes: Pooled Analysis of Clinical Trials from Across the COPD Portfolio

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Background

- Measurement of lung function by spirometry (forced expiratory volume in 1 second, FEV_1) is routinely used to evaluate the efficacy of bronchodilators
- However, evaluation of patient's outcomes is also important as it reflects the patient's quality of life
- Previous studies have shown that FEV_1 can be a good predictor of future morbidity, and mortality, patient reported outcomes (PROs) and exacerbation frequency[1,2]; however, they did not include information on COPD patients treated with a long acting β_2 agonist/long acting muscarinic antagonist (LABA/LAMA) combination

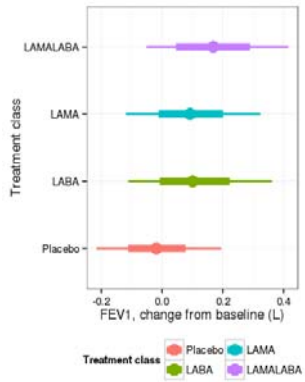
Objectives

- To characterize the correlation between FEV_1 and patient outcomes assessed with the St. George's respiratory questionnaire (SGRQ) in COPD patients treated with LABA (Salmeterol, Formoterol and Indacaterol), LAMA (Tiotropium and Glycopyrronium) and LABA/LAMA dual bronchodilator, QVA149 (fixed-dose combination of Indacaterol and Glycopyrronium)

Data

- Data was pooled from twenty-three randomized, parallel-group, placebo- or active-controlled studies (3 to 18 months duration; 23,213 patients, **Figure 1**) on FEV_1 and patient outcomes in COPD patients
  - Mostly moderate (45%) or severe (52%) patients, 54% were using inhaled corticosteroids, 35% had reported an exacerbation in the prior 12 months, average predicted FEV_1 at baseline was 44%
  - Two exacerbation studies were included with more severe patients (>98% patients with prior exacerbation; mean FEV_1 at baseline at ~35% of predicted)

Figure 1: Improvements in trough FEV_1 upon treatment



Point, thick line and thin line indicate the median and the 50 and 80 percentiles of the response in the pooled population

Methods

- The pooled data was analyzed using descriptive statistics of correlations. Correlation between FEV_1 and SGRQ were presented graphically
- Regression modeling was performed to determine, if changes in FEV_1 can predict improvements in patient outcomes observed for different treatment options
  - Linear longitudinal model were used that described baseline, treatment efficacy and drift and included between subject variability

Covariate modeling in three steps

- Differences between studies, treatment classes and treatments were included in the initial base model as fixed effects
- Predictors of treatment efficacy were systematically tested for inclusion, including interactions differentiating predictors by treatment class
  - Categorical predictors: Any exacerbation in the prior 12 months; Severity of disease (GOLD 2005); Smoking history; Inhaled corticosteroids; Sex
  - Continuous predictors: Age; weight; SGRQ at baseline; FEV_1 at baseline; rescue medication use at baseline; BDI; Predicted FEV_1; FEV_1 baseline, percent of predicted FEV_1; reversibility SABA (%)
- Inclusion of FEV_1 changes from baseline as predictor for SGRQ. The effect of positive and negative changes in FEV_1 on SGRQ was estimated with separate regression coefficients
- Evaluation of model quality using goodness of fit plots including evaluation of residuals as a function of study, treatment and time, and assessment of trends in random effects as a function of treatment, study and potential predictors

Results

Summary statistics showed statistically significant correlations between FEV_1 change from baseline and SGRQ

- Compared to patients with small response in FEV_1, patients with larger response in FEV_1 from baseline had on average better SGRQ (**Figure 2**)
- There was no evidence of a plateau effect; any further increase in FEV_1 response translated into further improvements in SGRQ

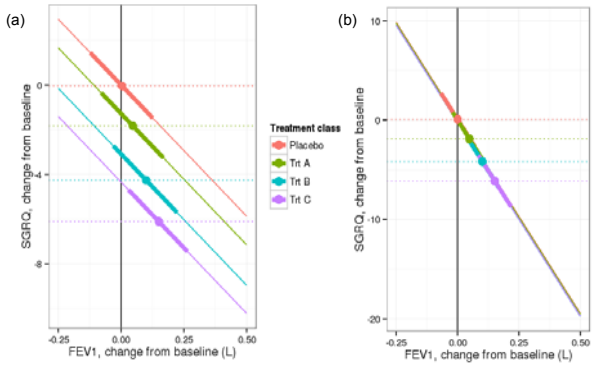
Regression modeling was performed to determine, if changes in FEV_1 predict improvements in patient outcomes observed with different treatment options

- Models were fitted using FEV_1 change from baseline as a predictor for SGRQ change from baseline
- Model based predictions compared efficacy of patients receiving active treatment and either
  - Showing no response in FEV_1 or
  - With FEV_1 response typical for treatment class
- The model based analysis confirmed that part of the treatment effects is best explained by changes in FEV_1 from baseline (**Figure 3**). 30% of the change in SGRQ was explained by FEV_1 change from baseline.

Discussion

- FEV_1 is a measurement affected by measurement errors. Due to regression dilution bias[3], models and summary statistics that use FEV_1 as an explanatory variable to explain other outcomes are expected to underestimate the association between FEV_1 and other endpoints
  - A correction factor valid for simple linear models may be estimated as the ratio of the total variance of FEV_1 measurements divided by the between subject variability. For the FEV_1 data, this factor was approximately two as estimated from a model of the available longitudinal FEV_1 data
  - Data was simulated assuming a high association between FEV_1 and other outcomes and analyzed in the same way as the clinical data.
    - Predictions based on the resulting model (**Figure 4a**) known to represent a strong association between endpoints were similar to the predictions obtained from the models of the clinical data. The regression models showed that part of the efficacy in SGRQ is best explained by changes in FEV_1 upon treatment.
    - Simulating data assuming that FEV_1 is measured without error (no residual variability), results in a model that finds that the efficacy in SGRQ is entirely explained by changes in FEV_1 (**Figure 4b**)

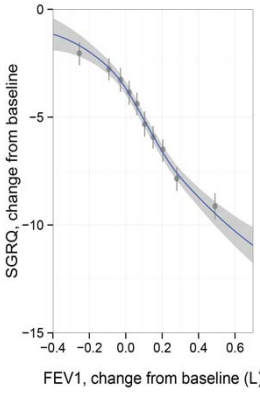
Figure 4: Analysis of data simulated assuming strong association between FEV_1 and SGRQ: Expected change in SGRQ following treatment and observed change of FEV_1 from baseline. (a) Data simulated assuming residual error of FEV_1 measurements of 0.15 L (b) Data simulated assuming no error of FEV_1 measurements



Simulation details: Treatments give a mean improvement of lung function (ΔFEV_1), μ_{trt}, of 0, 0.05, 0.1 and 0.15 L, respectively. Efficacy differs between patients, i, with standard deviation of 0.1L, $\mu_i \sim N(\mu_{trt}, 0.1)$. ΔFEV_1 has measurement error of 0.15 L, $\Delta FEV_i \sim N(\mu_i, 0.15)$. $\Delta SGRQ$ is equal to -40 times lung function, and has a measurement error of 6, $\Delta SGRQ_i \sim N(-40 \times \mu_i, 6)$. Alternative (b) assumes that ΔFEV_1 measures lung function without measurement error, $\Delta FEV_i \sim Norm(\mu_i, 0.0)$.

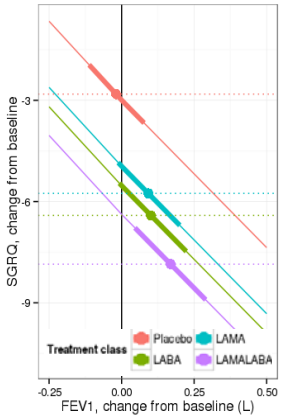
This suggests that the association of FEV_1 and SGRQ is strong. There is no evidence that factors other than lung function are important drivers of the efficacy of bronchodilators in improving patient reported outcomes

Figure 2: Change in SGRQ following treatment and observed change of FEV_1 from baseline



Blue line with band, loess regression line; Points with vertical line: mean with 95% CI of improvements in SGRQ for patients grouped into deciles of FEV_1 response.

Figure 3: Model based analysis: Expected change in SGRQ following treatment and observed change of FEV_1 from baseline



Thin lines: model predictions;
Thick lines and point: representative patient population for given treatment (median and 50% PI of FEV_1 change for treatment class)

Conclusions

- There is a statistically significant correlation between the average change in FEV_1 from baseline and SGRQ
- Change in FEV_1 has been shown to be a predictive marker in assessing the effectiveness of COPD treatment
- Due to variability of FEV_1 measurements, correlations with other endpoints are underestimated. Efficacy in SGRQ may be primarily due to bronchodilation which is measured by FEV_1

References

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