Chronic Obstructive Pulmonary Diseases:
Journal of the COPD Foundation

Editorial

Forced Expiratory Volume in One Second and Patient-Reported Outcomes: Closer Than You Think

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Abbreviations: chronic obstructive pulmonary disease, **COPD**; forced expiratory volume in 1 second, **FEV_1**; patient reported outcomes, **PROs**; St. George's Respiratory Questionaire, **SGRQ**; transition dyspnea index, **TDI**

Citation: Donohue JF. Editorial: Forced expiratory volume in 1 second and patient-reported outcomes: closer than you think. *Chronic Obstr Pulm Dis (Miami)*. 2016; 3(2):512-514. doi: http://dx.doi.org/10.15326/jcopdf.3.2.2016.0144

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Keywords:

forced expiratory volume in 1 second; FEV_1; patient reported outcomes

Current guidelines for chronic obstructive pulmonary disease (COPD) now recommend that lung function as measured by forced expiratory volume in 1 second (FEV_1) be measured alongside patient-reported outcomes (PRO) in clinical trials of inhaled bronchodilators. Important elements of COPD management are based on symptoms, severity, activity limitations or health status. All are relevant to the approval process and clinical use. Future risk of disease progression, particularly exacerbations, must also be considered for management of stable COPD and for consideration by policy makers and payers.

The meta-analysis in this issue of *Chronic Obstructive Pulmonary Diseases: Journal of the COPD Foundation* by de la Loge and colleagues[1] explores the relationship between trough FEV_1, FEV_1 area under the curve and PROs including St. George's Respiratory Questionnaire total score (SGRQ), transition dyspnea index (TDI) and exacerbation rates.

In this analysis, the quantity of 24 weeks duration-random controlled trials was 52 and the number of participants over 62,000; an impressive undertaking. The findings include a large negative correlation (R_1 0.68) between trough FEV_1 and SGRQ. Improvement of 100ml in FEV_1 corresponded to a 5.9 point reduction in SGRQ. The weighted correlation coefficient of trough FEV_1 with TDI, exacerbations rate (all), and with moderate to severe exacerbations are also all $p>0.05$. The conclusion is that a strong association exists between changes in spirometric measurements and changes in PROs.

But historically, while relationships exist at the clinical trial level, at the individual level predictions of COPD outcomes based on trough FEV_1 are not possible for a given patient due to the substantial between and within patient variability of these end points. This is evidenced in some studies by the limited magnitude of correlation coefficients despite significant p values.

What can physicians, policy makers, payers and patients take from these and other studies using large databases and meta-analysis? If FEV_1 is the primary outcome in pivotal clinical trials of bronchodilators, can we infer from a robust change in FEV_1 that exacerbation rates and hospitalization rates will decline while health-related quality of life and symptoms will improve?

The answer is still no; at least not yet. The authors and others clearly point out that a major limitation is that individual patient data is unavailable and these meta-analyses are conducted on study level data. In the future, hopefully the individual data will be available for

large clinical trials and in the public domain. Another limitation of all of these studies is that not all include all the end points of interest.

Other groups have correlated change in lung function with patient outcomes in COPD. In a pooled analysis from 3 studies of 3313 patients, TDI and change in SGRQ improved at all time points with increasing positive change in FEV_1.[2] Also, exacerbation rates over the study duration declined, $p>0.01$. However, individual level correlations were 0.03-0.18 while cohort level correlations were 0.79-0.95. At 28 weeks a 100ml increase in FEV_1 was associated with improved TDI (0.46), change in SGRQ (1.3-1.9) and a 12% decrease in exacerbation rate. Adjustments for baseline covariant seem to have little impact on the relationship between delta FEV_1 and outcomes.

More recently, pooled longitudinal data from 23 randomized studies (n=23,313) explores the relationship of these endpoints using correlations of data summaries and model-based analysis: generalized linear mixed effects regression modelling to determine if change in FEV_1 could predict patient outcomes with different treatments.[3] One intriguing finding was that no evidence of a plateau effect was observed such that patients with the greatest improvement in trough FEV_1 had better SGRQs and TDI scores, fewer exacerbations and used less rescue medication. The combination of long-acting beta-agonists/long-acting muscarinic-antagonists produced robust changes in FEV_1 and had greater effects on the PROs than mono therapies. Does this imply that maximizing lung function will lead to greater PROs? This question remains to be answered by randomized prospective studies.

The relationship of change in lung function, SGRQ and economically significant outcomes of exacerbation and health resource utilization are equally of interest.[4] These results and those of de la Loge offer providers and players a broader picture of the relationship between FEV_1 to inform clinical and formulary decisions while stimulating new research questions for future prospective studies.

References

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