

Treatments Based on Phenotypic Variants in Chronic Obstructive Pulmonary Disease

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Referring physicians may ask, “My patient with COPD is on her inhalers, so why does she continue to complain of worsened shortness of breath?”

Chronic Obstructive Pulmonary Disease (COPD) is characterized by progressive airflow limitation that is not fully reversible. Patients are stratified into low and high risk based on severity of airflow limitation (GOLD stages) and/or number of annual exacerbations [1]. Although COPD is the fourth leading cause of death, it is still under-diagnosed and frequently misunderstood [2,3]. Even when individuals have been diagnosed appropriately with COPD, the phenotypic variants (eg. emphysema, chronic bronchitis, etc.) may not be fully appreciated. Even within the same phenotypes, there is heterogeneity with symptomatology, physiological parameters and radiographic appearance. Ultimately, this may lead to sub-optimal management resulting in increased rate of exacerbations, disease progression and ultimately death.

Evaluation of the overall health of a COPD patient is shifting focus towards utilizing both subjective (St. George’s respiratory questionnaire, COPD Assessment Test, modified Medical Research Council (MMRC) dyspnea scale) and objective physiological parameters (spirometry, lung volumes, diffusion capacity, 6-minute walk distance) [4]. This provides an integrated evaluation of symptom burden and risk of exacerbation and mortality.

There is ample evidence for the association of COPD exacerbations and decline in lung function [5]. Importantly, it has been shown that successive severe exacerbations are more frequent, intervals between exacerbations are less (“clustering of exacerbations”) and severity of the exacerbation increases following the first severe exacerbation [6]. The major contributing risk factor for frequent exacerbations in all GOLD stages is a history of exacerbation [7]. Therefore, key strategy to successful management of COPD is a concerted effort to reduce exacerbation rates.

A number of trials have evaluated therapies to either reduce decline in lung function or reduce exacerbation rates [8-12]. However, trends in lung function decline were not significantly better in the treatment groups compared to the placebo group. With respect to the UPLIFT and TORCH studies, the treatment groups did have a 14-16% reduction in exacerbation rates. A potential criticism of these studies is that all phenotypes were lumped together for analysis. Future studies will most likely delve into therapeutic benefits in specific sub-populations.

Nonetheless, general recommendations remain to counsel patients on tobacco cessation, remain updated on immunizations, enroll in pulmonary rehabilitation and be on combination therapy with a long acting beta₂ agonist (LABA), Long Acting Muscarinic Antagonists (LAMA) and inhaled corticosteroids [1]. However, not all COPD is the same and perhaps should not be treated the same. This may be illustrated by the studies with roflumilast. Roflumilast, a phosphodiesterase-4 inhibitor, reduces airway inflammation. In two randomized clinical trials in a bronchitic COPD phenotype, comparing roflumilast 500 µg once daily to placebo over a 52-week period, FEV₁, FVC and mid-flow volumes improved along with a 16% reduction in exacerbations [13,14]. These effects were independent of concomitant inhalation medications or smoking status.

With respect to α₁-antitrypsin (AAT) deficiency, augmentation therapy is an additional therapeutic regimen that has been evaluated, but not administered consistently. Augmentation therapy is recommended in patients with α₁-antitrypsin (AAT) deficiency with serum AAT levels <11.0 µM and FEV₁ between 25-30% predicted at the lower limits and 65-80% predicted at the upper limits [15,16]. Although treatment with augmentation therapy has not reduced lung function deterioration, or frequency of exacerbation, it has reduced the severity of exacerbations [17]. An additional randomized controlled trial addressing the question of mortality benefits with augmentation therapy has recently ended enrollment and we look forward to results [18].

Lung volume reduction surgery has been a therapeutic option in selected patients with heterogenous lung involvement in emphysema. It improves dyspnea, lung function, exercise tolerance and prolongs life in selected patients [19]. It is not benign however. Perioperative death and post-operative complications have led to less invasive procedures to allow for similar benefits while minimizing risks [20,21]. Endobronchial one-way valves (EBV) are being utilized to achieve similar goals without the need to undergo surgery. EBVs are reserved for advanced heterogenous emphysema. Successful placement of EBV has been shown to improve lung function, dyspnea and exercise tolerance, but exacerbation episodes were more frequent post procedure compared to the control group who received standard medical therapy [22]. It has been proposed that the EBV itself may not be the contributing factor to developing an exacerbation as much as self-discontinuation of inhalation therapies.

In summary, it is proven that pulmonary rehabilitation, smoking cessation and preventive immunizations are beneficial in all sub-types of COPD. We know that exacerbations greatly contribute to disease progression, increase subsequent exacerbation severity and frequency, profoundly limit functional capacity and increase mortality. Future trials require re-evaluation of the currently recommended combination therapies with LAMA, LABA and ICS in specific subpopulations. A number of considerations should be taken into account when evaluating the status of the COPD patient. Most important, health care providers should be proactive in identifying the COPD phenotype and make attempts to limit exacerbation events based on targeted therapies. Hopefully molecular profiling can also assist us in identifying COPD subtypes to better provide targeted therapies.

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Received June 03, 2013; Accepted June 05, 2013; Published June 07, 2013

Citation: Afshar K (2013) Treatments Based on Phenotypic Variants in Chronic Obstructive Pulmonary Disease. J Pulm Respir Med 3: e128. doi:10.4172/2161-105X.1000e128

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