

Biomarkers in Chronic Obstructive Pulmonary Disease

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Currently, with exception of lung function tests, there are no well validated biomarkers or surrogate endpoints that can be used to establish efficacy of novel drugs for chronic obstructive pulmonary disease (COPD). However, the lung function test is not an ideal surrogate for short-term drug trials because it (1) does not provide information regarding disease activity or the underlying pathologic process, (2) cannot separate the various phenotypes of COPD, (3) is not specific for COPD, and (4) is relatively unresponsive to known therapies that prolong survival. Accordingly, there are large-scale studies presently underway to identify novel biomarkers in COPD. In this article, we discuss the current barriers of biomarker discovery and propose possible criteria and methods for developing novel biomarkers in COPD.

Keywords: biomarker; COPD; drug discovery

The global burden of chronic obstructive pulmonary disease (COPD) is large, with more than 600 million people affected worldwide and nearly 3 million dying from this disorder annually. Dissimilar to other major causes of mortality such as heart disease and HIV/AIDS, there are few, if any, pharmacologic therapies to prolong survival in COPD (1, 2). The current drug therapies are only modestly effective in relieving symptoms and improving quality of life, and most were developed as anti-asthma therapies. There are many promising targets for new drug discoveries in COPD; however, drug development is impeded by a lack of modifiable intermediate surrogates (i.e., biomarkers) to demonstrate promise of novel compounds in Phase II and early Phase III trials.

The National Institutes of Health defines biomarker as a “characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention” (3). Bucher and colleagues originally proposed two essential criteria for assessing the validity of biomarkers (4): (1) Is there a strong, independent, consistent association between the surrogate end point and the clinical end point? and (2) Is there evidence from randomized controlled trials that improvement in the surrogate end point with a drug consistently leads to improvement in the target (clinical) outcome? In COPD, these criteria can be extended to five essential questions (Table 1). The U.S. Food and Drug Administration indicates that at the moment “with the exception of lung function tests, there are no well-validated biomarkers or surrogate endpoints that can be used to establish efficacy of a drug for COPD” (5).

Accordingly, therapeutic trials in COPD have largely relied on forced expiratory volume in one second (FEV₁) as the

primary endpoint. FEV₁ is relatively easy to obtain, highly reproducible, and tracks health outcomes in COPD. However, FEV₁ is not an ideal surrogate for short-term drug trials because it (1) does not provide information regarding disease activity or the underlying pathologic process; (2) cannot separate the various phenotypes of COPD; (3) is not specific for COPD, as it is modified by common co-morbidities such as chronic infections, heart failure, or neuromuscular diseases (6, 7), and lung conditions such as asthma and pulmonary fibrosis; and, most importantly, (4) is relatively unresponsive to known therapies that prolong survival (e.g., supplemental oxygen) or other clinical outcomes in COPD (8–10). In addition, acute changes in FEV₁ after bronchodilators, “bronchodilator reversibility,” is not related to subsequent prognosis in COPD (11). FEV₁ is thus a good marker for risk stratification and prognosis, but a suboptimal surrogate for assessing the therapeutic potential of novel compounds. Exacerbation may also be considered a “biomarker.” While it is a good biomarker for intermediate to long-term studies, it has limited utility in short-term studies because exacerbations have seasonal variability, which may not be fully captured in short-term (<1 yr) studies. Furthermore, there is no consensus on the operational definition of an exacerbation, making cross-comparisons between studies difficult. With the advent of multi-detector row (high-resolution) computed tomography (CT), there is a growing interest in using CT scanning as a biomarker in COPD studies. Although promising, there is a scarcity of therapeutic trials using CT scanning to determine its usefulness as a biomarker in COPD. A more detailed discussion of CT scanning and other imaging modalities is provided by Coxson and coworkers (12).

COPD is undoubtedly an umbrella term, and it seems unlikely that all patients with COPD have the same underlying disease processes; thus, there is a need for differential treatment of different subgroups. A potential solution is to find modifiable biomarkers that can assist in drug development and distinguish subgroups of COPD. In theory, biomarkers can be obtained from any source. In COPD, the most logical source is the lung. Investigators have used exhaled breath condensates, exhaled volatile gases, induced sputum, and bronchial biopsies and lavages as noninvasive or minimally invasive methods of obtaining representative lung samples from which to develop biomarkers (9). While intuitively appealing, the development of lung-based biomarkers has been impeded by the invasiveness of procedures (e.g., bronchoscopy), poor sensitivities of tests (e.g., exhaled breath condensate measurements are often below the level of detection), and difficulties of standardizing the measurements from less invasive sources (e.g., induced sputum) (9). The latter may be improved by using standardized methods and by performing sequential sampling and averaging these results (13, 14). With the growing awareness of COPD as a systemic disease, there has been a shift in the emphasis of biomarker discovery toward blood specimens (15). Serum or plasma biomarkers are attractive because blood is readily available and their measurements can be easily standardized. To date, the best studied of these molecules are C-reactive protein and

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TABLE 1. PROPOSED CRITERIA FOR DEVELOPING NOVEL BIOMARKERS OR OTHER SURROGATE MARKERS IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE

1. Is there a strong biological plausibility in terms of its role in the pathogenesis of disease?
2. Is there a strong, consistent and independent association between the biomarker and chronic obstructive pulmonary disease?
3. Is there a strong, independent association between the biomarker and hard clinical outcomes such as mortality and hospitalization?
4. Is there evidence from randomized controlled trials that the biomarker is modifiable by interventions?
5. Is there evidence from randomized controlled trials that changes in the biomarker status result in changes in an important (and accepted) clinical outcome (e.g. mortality, exacerbation, rate of decline in FEV₁, health status)?

fibrinogen (see Table 2). Nevertheless, there remains a paucity of robust data from large clinical studies demonstrating their relationship with health outcomes of interest such as mortality, exacerbations, and changes in FEV₁ over time (Table 2). Moreover, it is not entirely clear how (and if) the blood measurements relate to the underlying disease activity in the lungs and what their biological roles are in the pathogenesis of COPD. Furthermore, they may suffer from the same weaknesses as FEV₁ in reflecting disease consequences rather than disease activity. The data for other promising molecules are even scarcer (Table 2).

In response to this need, several large-scale clinical studies are underway to identify novel biomarkers. One such study is ECLIPSE (Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints), which is a 3-year longitudinal study to define the parameters that characterize subgroups and predict disease progression in more than 2,000 individuals with COPD and to identify biomarkers that may serve as surrogate endpoints (16). Others include SubPopulations and Intermediate Outcome Measures In COPD Study (SPIROMICS), which will follow several thousand patients with COPD across six U.S. sites and is sponsored by the National Institutes of Health (<https://www.fbo.gov/index?s=opportunity&mode=form&tab=core&id=fbab23d004>

TABLE 2. SELECT CANDIDATE PLASMA OR SERUM BIOMARKERS THAT HAVE BEEN REPORTED TO BE ASSOCIATED WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE OUTCOMES IN LARGE CLINICAL STUDIES

Biomarker	Mortality	Exacerbation	FEV ₁ Decline	Health Status
CRP	Yes (18, 19)	Yes (20)	Uncertain (21)	Yes (22)
MMP-9	No data	Yes (23)	No data	No data
PARC	No data	Yes (20, 21)	No data	No data
MPIF-1	No data	Yes (20, 23)	No data	No data
ACRP-30	No data	Yes (20)	No data	No data
s-ICAM-1	No data	Yes (20)	No data	No data
Eotaxin-2	No data	Yes (20, 21)	No data	No data
IP-10	No data	Yes (20)	No data	No data
IL-1a	No data	Yes (20, 23)	No data	No data
TNF-R1	No data	Yes (20, 23)	No data	No data
IL-6	No data	Yes (20)	No data	No data
Serum Amyloid A	No data	Yes (24)	No data	No data
Fibrinogen	Yes (25)	Yes (26, 27)	Yes (27, 28)	No data
Surfactant Protein D	No data	Possibly (29)	No data	Yes (29)
CC-16	No data	No data	Possibly (31)	No data
Anti-elastin*	No data	No data	No data	No data
N-acetyl-proline-glycine-proline*	No data	No data	No data	No data

Definition of abbreviations: ACRP-30 = adipocyte complement-related protein of 30 kD; CC-16 = Clara Cell Secretory Protein-16; CRP = C-reactive protein; FEV₁ = forced expiratory volume in 1 second; IL-1a = interleukin-1; IL-6 = interleukin-6; IP-10 = interferon-inducible protein 10; MMP = matrix metalloproteinase; MPIF = myeloid progenitor inhibitory factor; PARC = pulmonary and activation-regulated chemokine; s-ICAM = soluble intercellular adhesion molecule; TNF-R1 = tumor necrosis factor receptor-1.

* Associated with emphysema phenotype (32, 33).

f33852a1942ba84e6b42a7and_cview=0) and COPDGene project (<http://www.copdgene.org/>), which will enroll more than 10,000 current and ex-smokers to identify biological risk factors for developing COPD. With these and other studies, there is renewed optimism in finding novel biomarkers that will accelerate the pace of both disease understanding and drug development and reduce the growing burden of COPD across the world, which in just few more years will be the third leading cause of mortality worldwide (17).

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