COPD Biomarkers as tools for decision making in early clinical development

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• COPD Biomarkers
  • Examples:
    A. Prognostic: Biomarkers for disease progression
    B. Pharmacodynamic: LPS challenge
    C. Predictive: Eosinophil count
    D. Surrogate: CompEx: Proxy for exacerbation

• Final comments
COPD, is defined as:

"a common, preventable and treatable disease (...) characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung".

Disease progression is described using Gold stages 0, 1, 2, 3. (at risk, mild, moderate and severe). Usually treatments concern stages 2-3.

Endpoints: Spirometry (FEV1) - Exacerbations – Imaging, QoL. In general, Low correlation between these.

Exacerbations are acute deteriorations triggered by e.g. bacterial and viral pathogens. They accelerate disease progression and have major implications on quality of life, morbidity and mortality. Exacerbations are rare occurrences so trials need to be long and/or large.

Unlike Asthma, no advanced therapy exists for COPD and it is believed that Biomarkers may allow for better understanding of the disease and the development of new therapies.
Biomarkers as Tools for Decision Making in Early Clinical Development

- Biomarkers are used to inform various types of decisions in early clinical development.
- We will present four such examples.
Types of biomarkers

Measured prior to therapy

Prognostic markers:
Indicate likely course of disease

Predictive markers:
Indicate likelihood of response to therapy

Measured after therapy

Pharmacodynamic markers:
Change in response to therapy

Surrogate- and Short Term Endpoints:
Represent clinical benefit, can be substitute for clinical endpoint
A: Prognostic biomarkers for lung function decline
Disease stages: Lung function decline

Disease stages are described using Gold stages 0, 1, 2, 3.

Biomarkers may allow for better understanding of the disease and the development of new therapies already at an early stage of the disease.

In a longitudinal study conducted in Denmark (CBO*) with annual visits between 2005 and 2009, lung function decline was followed in a group of healthy smokers and ex-smokers with a history of more than 20 pack years. The overall rational for the study was to determine the risk of smokers to develop cardiovascular disease, lung cancer and/or COPD.

Multivariate (PLS-DA) analysis using the blood biomarker ratio [(ApoD/MMP9)/(E-selectin) identified rapid FEV1 decliners in the GOLD 0 smoker group with at least 80% accuracy.
Biomarkers for disease progression: a HMM Bayesian approach

- HMM is a stochastic process \( \{X_t, Y_t\}_{t=0}^T \).
- \( \{X_t, Y_t\}_{t=0}^T \) is a hidden Markov chain (unobservable).
- \( \{Y_t\}_{t=0}^T \) is a sequence of observable independent random variables such that \( Y_t \) depends only on \( X_t, t = 0, 1, ..., T \).

\[
Y_{i,t|X_t=x_t} = \beta(x_t) Y_{i,t-1} + \mu(x_t) + \varepsilon_{i,t}.
\]

Disease stages

Biomarkers

Serum PRG4 is an important biomarker for supporting the COPD diagnosis and relates to the decline in lung function in patients with COPD.
B: Pharmacodynamics markers in COPD
Can a new compound prevent acute exacerbations of COPD?

The effect of a novel drug on lung inflammation is believed to correlate with effects on systemic biomarkers of inflammation. These markers are associated with risk of COPD exacerbations.

LPS challenges have been proposed as models for testing the mechanism of action of drugs that aim to reduce the frequency of exacerbations in COPD.

A Phase 1b proof of mechanism trial based on an LPS challenge, i.e. inhalation of an endotoxin lipopolysaccharide (LPS) that induces a neutrophilic airway inflammation.

Data from a competitor suggested that their (similar) compound achieved 25% reduction in Neutrophil differential under similar conditions.

- We use this effect (25% reduction) as our Target Value (TV).
- We also fix the Lower Reference Value to LRV to 10% reduction (TPP).
Go/No Go criteria for neutrophil differential

Go/No Go criteria for neutrophil differential

The observed level of reduction turned out to be 56% indicates a clear GO.

AZD7624, an inhaled p38 inhibitor for COPD, attenuates lung and systemic inflammation after LPS Challenge in humans
Naimish Patel, et al
• What if we are in the "Think" zone? Additional biomarkers could be used.
• How extend to multivariate case? MCDA.
• Sample size can be chosen as to get good decision criteria rather than statistical power.
C: Predictive biomarkers in COPD
Blood eosinophils

• Eosinophils:
  – A type of white blood cell
  – In some COPD patients, eosinophils contribute to inflammation that promotes airway obstruction
  – easy and reproducible to measure

• The level of eosinophils in blood can be predictive of the response to treatment with inhaled corticosteroids (ICS) to prevent exacerbations

Are blood eosinophil counts helpful in predicting patient responses to inhaled corticosteroids in COPD?

Best Practice Journal – Issue 74
Data from 3 AZ RCTs in patients with COPD with a history of exacerbations.

In patients treated with formoterol, blood eosinophil count predicts exacerbation risk and the clinical response to ICS.

In 79% of the population studied, there is benefit of ICS+LABA to reduce the risk of future exacerbations.

Patients with low levels constitute a group with an unmet need for better treatment.

Blood eosinophils, example 2

Proof of Principle study with AZD7624 in patients with COPD on at least ICS+LABA.

D: Surrogate Biomarkers for COPD
Symptom-based surrogate endpoints

• Clinical trials in COPD with moderate/severe exacerbations as the main endpoint
  – Large and lengthy
  – Troublesome in early clinical development

• Establish a composite endpoint, adding events defined by mixed diary variables
  – Capture clinically relevant disease deteriorations
  – Surrogate for exacerbations, predictive of effect in Ph3 trials
COPDCompEx: A Novel Composite Endpoint to Accelerate Early Clinical Development of New Agents for Treatment of COPD

• The algorithm defining diary events using
  – morning PEF
  – evening PEF
  – total reliever medication use
  – COPD symptoms
  reflected the treatment effect on exacerbation with the best statistical power.

• A decreased sample size by at least 50% on average (range 35%-88%, except for one trial).

• Enables shorter (3m) and smaller trials.
How can we make sure that an effect on early phase endpoints reflects a treatment effect in Phase 3?

- We have explored joint models of different endpoints in COPD
  - Joint modelling example: linking FEV1 and exacerbations

\[ \Delta \text{FEV1}_i(t) = \underbrace{ns_{\text{fixed}}(t) \cdot \beta}_{\text{fixed effect spline}} + \underbrace{ns_{\text{rand}}(t) \cdot b_i + \varepsilon_i(t)}_{\text{random effect spline}} \]

\[ \lambda_i(t) = \lambda_0(t) \cdot \exp(x_i^T \cdot \xi + \alpha \cdot m_i(t)) \]

Fixed effect

Random effect

Association parameter
How can we make sure that an effect on early phase endpoints reflects a treatment effect in Phase 3?

Different estimation methods explored

We plan to expand to look at PROs and biomarkers

Final comments

We have seen examples demonstrating existing and potential use of Biomarkers and surrogate endpoints in early drug development possibly leading to

- New treatment paradigm: treating rapid decliner patients at an early stage.
- Better understanding of treatment effect in terms of disease progression.
- Better decision making in early clinical drug development by using proof of mechanism biomarkers to trigger further clinical activities.
- Tailor treatment to fit patient needs by e.g. taking eosinophil levels into account
- New surrogate endpoints could potentially lead to shorter, smaller and yet more conclusive clinical trials.
- Use of short term endpoints can be used to achieve adaptive designs

But more validation is needed and rigorous use of Statistical methods is necessary!