Phenotyping and Endotyping in COPD: The Search for Targeted Therapies

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Chronic obstructive pulmonary disease (COPD) is a heterogeneous condition, with patients displaying varying pathophysiological and clinical features including chronic predominantly neutrophilic inflammation of the airways and irreversible airflow obstruction. This leads to emphysematous destruction of lung tissue and deterioration of pulmonary function. The most common cause is cigarette smoking. Genetics, childhood lung development and environmental exposures also play a role. The clinical presentation ranges from exertional dyspnea and respiratory tract infections, to progressive severe exacerbations of the disease that may require hospitalisation, reduced exercise tolerance, respiratory failure, and associated co morbidity including pulmonary hypertension, sleep disordered breathing, depression and an increased risk of lung cancer. It remains the third leading cause of death worldwide.1

To date, treatment has focused predominantly on guideline directed therapy primarily concentrated on symptom management and treatment of exacerbations with inhaled bronchodilator and corticosteroid therapy, an often chronic reliance on oral corticosteroids and frequent antibiotics. Adjunctive, non-pharmacological therapies including oxygen prescription, non-invasive ventilation, and pulmonary rehabilitation are also implemented. The identification of COPD endotypes, with distinct underlying disease mechanisms may allow for targeted treatment strategies directed towards specific biological pathways.

COPD Phenotypes

COPD phenotypes refers to a single or combination of disease attributes that describe similarities between subgroups of COPD patients based on clinically significant parameters. Ideally individuals grouped within a clinical phenotype should demonstrate a similar clinical trajectory and response to treatment due to a common underlying biological mechanism (i.e. endotype).2 The idea of phenotyping within COPD is well established, with many textbooks traditionally describing the ‘blue bloater’ versus the ‘pink puffer’, of course referring to those with chronic bronchitis and emphysema respectively. In fact, as far back as 1989, Snider classified airflow obstruction into three groups via a non-proportional venn diagram which largely still hold true; asthma, emphysema and bronchitis.2 Despite much analysis, it remains challenging to accurately and consistently define phenotypes among the COPD cohort.

Spirometry indices, FEV1/FVC ratio <70%, are used to diagnose, and the decline in FEV1 used to assess the severity of disease. A bronchodilator response of >15% and 200ml increase in FEV1 may indicate an asthma-COPD overlap phenotype.4 Radiological phenotyping with computed tomography (CT) assessment of small airway disease versus emphysema would offer an objective measure of parenchymal disease that correlates well with histopathologic findings and is predictive of the degree of expiratory airflow obstruction, however allocation of resources in most centers will not allow for CT use for categorization of COPD as the primary indication.5 The frequency of pulmonary exacerbations lends itself to a clinical phenotype; the frequent exacerbator. Defined as >2 exacerbations/year, this phenotype is associated with higher mortality and healthcare utilisation.6 Exacerbation predominant COPD is recognized by the global initiative for chronic obstructive lung disease (GOLD) and is used in their classification system (GOLD C/D; >2 exacerbations/yr or 1 exacerbation requiring hospitalization) and hence, influences their treatment algorithm.6

While historical phenotypes based on clinical characteristics and newer emerging phenotypes are becoming increasingly recognized, a lack of correlation to specific disease mechanisms underpinning these phenotypes has limited their impact regarding personalized therapies thus far.

COPD Endotypes

COPD endotypes imply known molecular mechanisms leading to the clinical phenotype of the disease. Often, these are recognized by associated biomarkers that are reflective of the underlying biologic processes.

Genetic endotypes

The best described endotype in COPD is alpha one antitrypsin (AAT) deficiency. AAT is a protease inhibitor (Pi). In healthy individuals, AAT acts to inhibit destruction by the serine protease neutrophil elastase, an enzyme which attacks lung elastin and damages bronchial and alveolar wall integrity.

The gene that encodes AAT is SERPINA1 and is located on the long arm of chromosome 14. The normal allele is referred to as ‘M’. Thus “Pi*MM” indicates homozygosity for the normal allele. “Pi*ZZ” refers to homozygosity for the “Z” allele, the most common mutation in the SERPINA1 gene, associated with very low levels of AAT and a very high risk of developing rapidly progressive...
emphysema. Further point mutations include the "S" allele, homozygosity for this infers moderately reduced levels of AAT without increased risk of emphysema, however compound heterozygosity such as "Pi*MZ" or "Pi*SZ" leads to an increased risk of emphysema, particularly in smokers. Individuals with the ‘null’ allele (Pi*N) have undetectable levels of plasma AAT and therefore are at highest risk of severe pulmonary manifestations. This phenotype is thankfully the least common.7

AAT deficiency is under-recognised and clinicians should consider it as a potential diagnosis in all adults with persistent airflow obstruction but especially in adults who develop emphysema at a young age (<50), emphysema in the absence of smoking history or other environmental exposures, lower lobe predominant emphysema, adult onset asthma and unexplained bronchiectasis. Bear in mind that patients may present with hepatic or cutaneous manifestations of the condition also. Diagnosis is confirmed by testing serum levels of AAT (<11mmol/L = severe deficiency), followed by confirmatory genotyping alongside spirometry and pulmonary imaging.

Treatment with intravenous augmentation therapy (pooled human alpha 1 proteinase), aims to elevate the serum and interstitial levels of AAT and has been proven to slow the rate of lung density loss on CT. Treatment is recommended for patients with confirmed deficiency of AAT with a severe genotype and in whom FEV1 is within 30-65% of predicted.6 8

**Inflammatory Endotypes**

Eosinophils are innate immune cells which are regulators of the type 2 immune response pathway. Eosinophils usually remain quiescent in blood until exposed to pro-inflammatory mediators such as IL3, IL5 and GM-CSF at which point they become activated and migrate to sites of inflammation. Once in the lungs, eosinophils release a range of pro-inflammatory cytokines, chemokines and growth factors which contribute to sustained inflammation and tissue damage.9 Eosinophilic inflammation occurs frequently in COPD and its use as an endotype is surpassing others given its clinical applicability. Airway eosinophils can be measured via sputum and bronchial mucosa sampling. However, studies show that peripheral blood eosinophilia (>0.3x10^9/L) correlated with an elevated sputum eosinophil count (>3%) in 70% of cases, hence blood eosinophils are accepted as a surrogate biomarker for airway eosinophilia.10

Eosinophilia in COPD is associated with an increased frequency of exacerbations, readmissions to hospital and accelerated disease progression. The evidence is compelling that this endotype demonstrates an exaggerated response to inhaled corticosteroids (ICS) and systemic steroids. Several post hoc analyses have demonstrated a slower decline in FEV1, reduced exacerbation rates and improved symptoms in patients with elevated eosinophil counts receiving ICS compared to those with lower eosinophil counts.1 The IMPACT trial (informing the pathway of COPD treatment) went on to prospectively demonstrate a greater reduction in exacerbation frequency in patients with eosinophilic inflammation (>150cell/μl) with the use of once daily therapy (ICS/LAMA/ LABA) compared with LAMA/LABA or ICS/LABA combinations.12

The body of evidence conferring the benefit of ICS in eosinophilic inflammation in COPD was reflected in the updated GOLD guidelines, 2019. Peripheral blood eosinophil count is now taken into account alongside the known ‘ABCDE’ classification. An ICS in conjunction with a LABA or LABA/LAMA is recommended for individuals with persistent dyspnea and eosinophils >0.3x10^9/L or those with eosinophils >0.1x10^9/L plus >2 exacerbations per annum, or one exacerbation requiring hospitalisation. Patients should be monitored for a response to treatment and adverse events such as pneumonia, which may prompt consideration of withdrawal of ICS.13

Several treatments targeting the eosinophilic pathway with monoclonal antibody therapies for eosinophil COPD are in development. Mepolizumab targets the IL-5 ligand and inhibits IL5 receptor signaling in eosinophils. It was approved as an adjunctive treatment in severe asthma with associated eosinophilia in 2015. In this group it has been shown to reduce exacerbation frequency, improve symptoms, improve FEV1 and reduced oral corticosteroid use. Initial studies on the use of mepolizumab in the eosinophilic COPD population did not show a statistically significant reduction in exacerbations or improvement in FEV1, however emerging Phase III data indicated an improvement in exacerbation rates in patients with elevated eosinophils and COPD.14 Phase III data collection is ongoing. Benralizumab targets the IL5 receptor and demonstrated similar clinical benefits in severe eosinophilic asthma as mepolizumab. With regards exacerbations, FEV1, corticosteroid use and symptoms. Phase II trials in the eosinophilic COPD cohort did not suggest an improvement in exacerbation rates but did demonstrate an improvement in FEV1 in COPD patients with elevated eosinophils allocated to benralizumab.15 Phase III trials are ongoing.

There is ongoing research into other pathways of innate and adaptive immune which undoubtedly contribute to the pathophysiology of COPD. For example, there is emerging evidence of a potential role of the type 17 helper T cells (Th 17) and their pro inflammatory cytokines; IL-17A in the pathogenesis of COPD, more specifically the emphysematous phenotype.16 Similarly, while intermittent respiratory infections with viral and bacterial pathogens are a hallmark of COPD, bacterial colonization in sputum and bronchoscopy derived samples is well described. At a molecular level, this bacterial colonization and frequency of exacerbations may be linked to a defect of phagocytosis of bacteria by macrophages.17 Defects in IL-22 have been suggested as partly responsible for this lack of inflammatory resolution and bacterial colonization.18 These theories are underdeveloped and require further analysis.

**Conclusion**

COPD is phenotypically heterogeneous. An improved understanding of the underlying biological mechanisms which drive the chronic inflammation associated with the disease is required to aid the identification of endotypes. In recent years, progress has been made with the recognition of eosinophilic COPD as an endotype and its inclusion in treatment guidelines. Currently, there are number of promising areas of research into the identification of additional endotypes and potential biomarkers which will need refinement and longitudinal assessment of their viability and stability over time as therapeutic targets.

References on request