Emerging role of Biologics in COPD

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Chronic obstructive pulmonary disease (COPD) is the leading cause of morbidity and mortality worldwide with significant socio-economic burden. The global prevalence of COPD is estimated at 10.3%, with around three million deaths annually. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2023 defines COPD as a heterogeneous lung condition characterized by chronic respiratory symptoms (dyspnoea, cough, sputum production and/or exacerbations) due to abnormalities of the airways (bronchitis, bronchiolitis) and/or alveoli (emphysema) that cause persistent, often progressive, airflow obstruction.(1)

COPD develops due to complex host-environment interaction in a genetically susceptible individual, with exposure to tobacco smoke, indoor/ outdoor pollutants, allergens, microbial pathogens that trigger a chronic airway inflammation leading to irreversible damage, fixed airflow obstruction and the consequent typical symptoms of COPD. The initial treatment involves bronchodilators- long acting beta agonists (LABA) and long acting muscarinic antagonists (LAMA), given as a single inhaler or a combination in symptomatic patients. Addition of inhaled corticosteroids (ICS) or systemic corticosteroids in patients with persistent symptoms or frequent exacerbations despite LABA+LAMA therapy and blood eosinophil count >300 cells/µl. However, long term use of corticosteroids have been associated with serious adverse effects including pneumonia, adrenal suppression, hypertension, cataract, glaucoma, osteoporosis. Hence with further research and understanding of the pathways involved, immune targeted novel biologics are emerging for treatment of COPD.(2)(3)

Airway inflammation in COPD- The inflammatory response in COPD involves both innate and adaptive immunity, with neutrophilic inflammation being predominant, eosinophilic inflammation is around 20-40%.(2)

Eosinophilic airway inflammation- The aetiology of eosinophilic airway inflammation in COPD is uncertain. Increased eosinophils in peripheral blood and sputum, like asthma is associated with a greater risk of future exacerbations. Following allergic sensitization, Th2 cells produce IL-4, IL-5 and IL-13. IL-5 is essential for survival and maturation of eosinophils, IL-4 and IL-13 promote IGE production from B-cells. CCR3 chemokines and other eosinophil chemoattractants, such as mast cell-derived prostaglandin (PG)D_2 are involved in recruitment of eosinophils in the lung mucosa.(2)

Neutrophilic airway inflammation- It is the most common inflammatory phenotype observed in COPD. The earliest clinical trials of biologics in COPD targeted specific steps in the neutrophilic pathways. The anti-neutrophilic agents that have been investigated include- anti IL-1, IL-17, IL-8, anti-CXCR2, and tumor necrosis factor-alpha (TNF-a). The results from these trials have demonstrated limited clinical benefits. Further, TNF-a inhibitors were associated with an increased risk of infection and malignancy. Anti-IL-8 and anti-CXCR2 therapies, demonstrated a small improvement in dyspnea, however, they were associated with an increased risk of infection. (4)

More recent trials have targeted T2 inflammatory pathways involving eosinophilic inflammation. Several T2 targeted biologics have been approved in patients with asthma, but such studies in COPD are few since eosinophilic inflammation are less common.(4)

Recent trials and targets for biologics in COPD

IL-5

IL-5 is a cytokine that regulates proliferation, maturation, migration, and effector functions of eosinophils. A Cochrane review of six randomised controlled trials comparing anti-IL-5 (Mepolizumab) and anti-IL-5 receptor (Benralizumab), with the primary objective of reduction in moderate to severe exacerbations demonstrated a reduction in the rate of exacerbation in a highly selective group of COPD patients with high blood eosinophil levels with frequent exacerbations. However, no improvement in lung function and quality of life was observed.(5)

There have been two randomized placebo-controlled trials- METREX and METREO to study the effects of mepolizumab in COPD patients with frequent moderate to severe exacerbations despite on triple therapy (LABA+LAMA+ICS). The primary end point being annual rate of exacerbations. In METREX, the intention-to-treat population with an eosinophilic phenotype were stratified according to blood eosinophil count (≥150 per cubic millimeter at screening or ≥300 per cubic millimeter during the previous year). In METREO, all patients had a blood eosinophil count of at least 150 per cubic millimeter at screening or at least 300 per cubic millimeter during the previous year. Patients were given mepolizumab (100 mg in METREX, 100 or 300 mg in METREO) or placebo, as a subcutaneous injection every 4 weeks for 52 weeks. The studies showed 18%-20% reduction in annual exacerbation rate as compared to placebo in subtype of COPD patients with eosinophilia. The time to first exacerbation was significantly longer in mepolizumab group than placebo in METREX but not in METREO trials. (6)

Benralizumab is an interleukin-5 receptor alpha–directed monoclonal antibody that induces rapid and substantial eosinophil depletion by means of antibody-dependent cellular cytotoxic activity. Two phase 3 randomized placebo-controlled trials in moderate to severe COPD patients with eosinophilic subtypes, did not show significant reduction in annual exacerbation rates. However, it did demonstrate significant reduction in blood and sputum eosinophilia, improvement in lung function and quality of life.(7)

IL-4 and IL-13

Dupilumab is a fully human monoclonal antibody that blocks the shared receptor component for interleukin-4 and interleukin-13, thus blocks the type 2 inflammation more broadly. The BOREAS trial was a phase 3 randomized placebo-controlled trial conducted at 275 sites across 24 countries, in patients with moderate to severe COPD on triple inhaler therapy (LABA+LAMA+ICS) with eosinophilic inflammation. Dupilumab 300mg or matching placebo was administered subcutaneously every 2-weeks for 52 weeks.(8)

Dupilumab significantly reduced the annual rate of moderate to severe COPD exacerbations [0.78 in the dupilumab group and 1.10 in the placebo group ($p< 0.001$)]. Dupilumab also resulted in significant improvement in lung function and quality of life measured by SGRQ score as compared to placebo.In comparison to studies conducted for biologics targeting IL-5 that showed mixed results with respect to COPD exacerbations, with no evidence of improvement in lung function or quality of life, the BOREAS trial confirms the role of IL-4,

IL-13 in the pathophysiology of COPD that extends beyond the role of IL-5 or eosinophils.(8)

IL-33/ ST2

IL-33 is a cytokine released from bronchial epithelial cells in response to allergens, microbes and air pollutants. IL-33 and its receptor ST2 have been implicated in airway inflammation and infection. Astegolimab, is a selective ST2 IgG2 monoclonal antibody that was assessed in the COPD-ST2OP trial. It was a single-center randomized, placebo-controlled phase 2a trial in patients with moderate to very severe COPD. There was no pre-specified eosinophil cut-off, but they had to have had at least 2 moderate to severe exacerbations in the previous 12 months. The treatment resulted in a non-significant reduction in the rate of exacerbation, but did improve health status compared to placebo. A larger study that uses information from this trial to determine an appropriate eosinophil cut-off and other inclusion criteria that can help evaluate whether this therapy may be useful for COPD patients.(4)

Itepekimab is a monoclonal antibody against IL-33, was assessed in a randomized placebo-controlled phase 2a trial in patients with moderate to severe COPD, who were current or former smokers. There was a nominally significant reduction in exacerbation and improvement in lung function in former smokers. Two phase 3 studies are undergoing to confirm the efficacy and safety profile of Itepekimab in former smokers with COPD.(4)

Tozorakimab is an anti IL-33 monoclonal antibody that has shown favourable safety and pharmacokinetic profile in small scale clinical trials. There are two ongoing phase 3 randomized clinical trials to evaluate the efficacy and safety of tozorakimab, administered subcutaneously in patients with COPD, who are former smokers, with history of exacerbations in the previous 12 months.(9)

Drug/ Target	Reduction in exacerbation	FEV1	Health status (SGRQ score)
Mepolizumab/ IL-5	18%- 20%	⟷	⟷
Benralizumab/ IL-5 R-alpha	⟷	+ improvement	+ Improvement
Dupilumab/ IL-4/IL-13	+ Significant reduction	+ significant improvement	+ significant improvement
Astegolimab /Anti ST2	Non-significant reduction		+ improvement
Itepekimab / IL-33	Mild reduction in former smokers	Mild reduction in former smokers	
Tozorakimab/ IL-33 (favourable safety and pharmacokinetic profle in phase 1)	Ongoing	Ongoing	Ongoing

Table 1. Results of randomized control trials of biologics in COPD. IL- interleukin, FEV1- Forced expiratory volume in 1 second. SGRQ-St George's respiratory questionnaire

Conclusion

COPD is a heterogeneous condition associated with persistent chronic airway inflammation. Biologics have been approved for treatment of severe eosinophilic asthma, but their efficacy in eosinophilic COPD have demonstrated mixed results. Corticosteroids are most effective in treatment of eosinophilic COPD, but recent trials have shown partial response to a definite subgroup of patients that warrants further studies into mechanism and pathophysiology of COPD. Although targeted therapies for neutrophilic COPD have shown negative results, several ongoing investigations of biologics targeting specific pathways of inflammation will provide further insight into patient selection criteria and hopefully reduce the need for corticosteroid dependence in patients with moderate to severe COPD.(2)(4)

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