

EMERGING ROLE OF BIOLOGICS IN COPD

Abstract

Chronic obstructive pulmonary disease (COPD) is characterised by chronic airway inflammation and fixed airflow obstruction. The mainstay of treatment involves bronchodilators with the addition of inhaled corticosteroids in non-responding patients with eosinophilic sub-type. The airway inflammation in COPD is mainly neutrophilic, around 20% is mediated by eosinophils via Th2 pathway. With further understanding of Th2-mediated airway inflammation in COPD, novel biologics targeting specific stages in the immune pathway including monoclonal antibodies are under research. Although several biologics have been approved for the treatment of severe bronchial asthma, their efficacy in the treatment of COPD is unknown. In this review, we discuss the different studies, trials and clinical outcomes 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, 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, and microbial pathogens triggering a chronic airway inflammation causing fixed airflow obstruction, and irreversible damage leading to the 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. An 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/ μ l, may be required. However, long-term use of corticosteroids has been associated with adverse effects including pneumonia, adrenal suppression, hypertension, cataract, glaucoma, and osteoporosis. Hence with further research and understanding of the pathways involved, immune-targeted novel biologics are emerging for the treatment of COPD.(2)(3)

I. AIRWAY INFLAMMATION IN COPD

Both innate and adaptive immune responses are responsible for inflammation in COPD, with neutrophilic inflammation being predominant, and eosinophilic inflammation around 20-40%.(2)

- 1. Eosinophilic Airway Inflammation:** The cause of eosinophilic airway inflammation in COPD is unclear. However, like asthma, eosinophilia in peripheral blood and sputum is associated with a higher risk of exacerbations. Following allergic sensitization, Th2 cells produce IL-5, IL-4 and IL-13. IL-4 and IL-13 promote IGE production from B-cells, and IL-5 is essential for the survival and maturation of eosinophils. CCR3 chemokines and eosinophil chemoattractants, including mast cell-derived prostaglandins are involved in the recruitment of eosinophils.(2)
- 2. Neutrophilic Airway Inflammation:** Is the most common inflammatory phenotype in COPD. The earlier clinical trials of biologics targeted specific pathways involved in neutrophilic inflammation, these include anti-IL-1, IL-8, IL-17, anti-CXCR2, and tumour necrosis factor-alpha (TNF-a). However, the results did not show significant clinical benefits and were associated with serious adverse effects, for example, TNF-a inhibitors were associated with a higher risk of infection and malignancy. Although anti-IL-8 and anti-CXCR2 therapies resulted in mild improvement in dyspnoea, they were associated with a higher risk of infection. (4)

Recent trials have targeted T2 inflammatory pathways leading to eosinophilic inflammation. Several T2-targeted biologics have been approved in patients with asthma, but such studies in COPD are few since eosinophilic inflammation is less common.(4)

II. RECENT TRIALS AND TARGETS FOR BIOLOGICS

- 1. IL-5:** IL-5 is a cytokine that regulates the proliferation, migration, maturation and effector functions of eosinophils. A Cochrane review of six randomised controlled trials comparing anti-IL-5 (Mepolizumab) and anti-IL-5 receptor (Benralizumab), demonstrated a reduction in the rate of moderate to severe exacerbation in a selective group of COPD patients with high blood eosinophil levels and 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 triple therapy (LABA+LAMA+ICS). The primary endpoint being reduction in the 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 millimetre at screening or ≥ 300 per cubic millimetre during the previous year). In METREO, all patients had a blood eosinophil count of at least 150 per cubic millimetre at screening or at least 300 per cubic millimetre 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 an 18%-20% reduction in annual exacerbation rate as compared to placebo in a subtype of COPD patients with eosinophilia. The time to first exacerbation was significantly longer in the mepolizumab group than placebo in METREX but not in METREO trials. (6)

Benralizumab is a monoclonal antibody directed against IL-5 receptor alpha, that induces rapid and marked eosinophil depletion via antibody-dependent cellular cytotoxicity. 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 a significant reduction in blood and sputum eosinophilia and, an improvement in lung function and quality of life.(7)

- 2. IL-4 and IL-13:** Dupilumab is a humanised monoclonal antibody that blocks the shared receptor component for interleukin-4 and interleukin-13, thus blocking type 2 inflammation more broadly. The BOREAS trial was a phase 3 randomized placebo-controlled trial conducted across 24 countries at 275 sites, 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 limited clinical benefits with respect to COPD

exacerbations, and no evidence of improvement in lung function and 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)

3. **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 evaluated in the COPD-ST2OP trial. It was a phase 2a single-centre randomized, placebo-controlled trial in patients with moderate to very severe COPD. The inclusion criteria required patients to have had at least 2 moderate to severe exacerbations in the past 12 months. The treatment resulted in a non-significant reduction in the rate of exacerbations, but did improve the health status as compared to placebo.(4)

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

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

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

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 profile in phase 1)	Ongoing	Ongoing	Ongoing

III. CONCLUSION

COPD is a heterogeneous condition associated with persistent chronic airway inflammation. Biologics have been approved for the treatment of severe eosinophilic asthma, but their efficacy in eosinophilic COPD has demonstrated mixed results. Corticosteroids are most effective in the treatment of eosinophilic COPD, but recent trials have shown partial response to a definite subgroup of patients that warrants further studies into the 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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