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Short Communication

Biologics Novel Therapy in Advanced COPD

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Chronic obstructive pulmonary disease (COPD) is a heterogeneous inflammatory condition which causes critical health concerns and along with socioeconomic burden. Even with the maximum inhaled therapy, oral anti-inflammatory, oxygen, noninvasive ventilation, and pulmonary rehabilitation COPD patients continue to have exacerbations leading to significant impairment of quality of life [1].

Biological agents refer to therapeutic agents that are used to manage inflammation, reduce symptoms, and prevent exacerbations in patients. The inflammation in COPD involves various biological agents, including inflammatory mediators, cytokines, and cells, which contribute to the disease pathophysiology [1,2].

Two clinical phenotypes at molecular level including eosinophilic and neutrophilic types which would be the target of focus to battles this crucial disease [13].

Type 1 (T1) neutrophilic inflammation is the primary inflammatory cascade in patients with COPD and can overlap with type 2 (T2) eosinophilic inflammation further associated with Th2 lymphocytes, innate lymphoid cell type 2 (ILC2) and interleukin- 13 (IL-13) [14,16].

Inflammatory mediators and biological pathways in COPD

COPD is overall an inflammatory cascade with crucial involvement of immune cells and the release of biological agents like as follows:

- **Cytokines:** These are signaling proteins that mediate inflammation. In COPD, elevated levels of pro-inflammatory cytokines like TNF-α (tumor necrosis factor-alpha), IL-8 (interleukin-8), IL-1β, and IL-6 are common. They are involved in attracting immune cells (neutrophils, macrophages) to the lungs, contributing to tissue damage, mucus production, and airflow obstruction [3].
- **Proteases:** Enzymes like matrix metalloproteinases (MMPs) and neutrophil elastase degrade the extracellular matrix, leading to structural changes in the lungs (emphysema) and increased mucus production [4].
- **Oxidative stress:** The lungs in COPD patients experience increased oxidative stress due to the continuous exposure to cigarette smoke, leading to the activation of inflammatory pathways [5].
- **Chemokines and growth factors:** These agents recruit and activate immune cells (e.g. macrophages, neutrophils) that perpetuate the inflammatory cycle, causing further damage [6].

Phosphodiesterase-4 (PDE4) inhibitors

- Roflumilast is a PDE4 inhibitor that reduces the production of inflammatory mediators, particularly in patients with chronic bronchitis. It works by reducing the breakdown of cAMP (cyclic adenosine monophosphate), thereby inhibiting inflammatory pathways [7].

Biological agents for treating COPD

In COPD treatment, biological agents are used primarily to target the underlying inflammation and further decrease exacerbations. They are often used for patients who have high levels of blood eosinophils that does not respond to standard treatment [8]:

- **Anti-IL-5 agents:** Interleukin-5 (IL-5) is responsible for activation of eosinophils [9]. Mepolizumab and Reslizumab are biological agents which reduces eosinophilic inflammation.
- **Anti-IL-4 and anti-IL-13 agents:** Interleukin-4 (IL-4) and interleukin-13 (IL-13) causes allergic inflammation, airway remodeling, and mucus production [10]. Dupilumab targets both IL-4 and IL-13.
- **Anti-TNF-α agents:** Tumor necrosis factor-a (TNF-α) contributes to airway inflammation and tissue damage. Infliximab and adalimumab, targets TNF-α [11].

Role of biological agents in COPD pathogenesis

COPD progression involves two key processes:

- **Chronic inflammation and oxidative stress:** Biological agents can help target these inflammatory pathways, reducing the overall inflammation and its harmful effects.
- **Airway remodeling and fibrosis:** Some biologic therapies aim to slow the process of airway remodeling (structural changes in the lungs), which contributes to long-term airway obstruction [15].

Current evidence

BOREAS trial postulated dupilumab as an advance therapy for moderate to severe COPD exacerbations with type 2 inflammation excluding asthma patients with blood eosinophil count of at least 300/mL. 52-week trial showed reduction in COPD exacerbations, lung function improvement and decrease clinical symptoms [12].

More studies would be beneficial for emerging evidence of different biological agents targeting various inflammatory molecular targets to battle the heterogeneity of COPD to improve health conditions and decrease healthcare cost burdens.

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