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Biologics in the Management of Chronic Obstructive Pulmonary Disease: Emerging Perspectives

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Chronic Obstructive Pulmonary Disease (COPD) is an Inflammatory Disease

Inflammation is at the core of multiple, highly variable, and interconnected pathological processes, which will eventually sow the seeds of chronic bronchitis and/or emphysema in exposed and susceptible individuals.[1] Low-grade chronic inflammation in these patients is acutely worsened during infectious, and to a lower extent, non-infectious COPD exacerbations.[2] Unfortunately, a large fraction of patients receiving contemporary anti-exacerbation prophylaxis–including that provided by inhaled combinations of long-acting β_2-adrenoceptor agonist (LABA), long-acting anti-muscarinic (LAMA), and inhaled corticosteroids (ICS) (triple therapy)–remain *frequent exacerbators*. These patients have at least two moderate episodes and/or one severe episode requiring hospitalization or an emergency department visit in the preceding year. Given their higher risk of disease progression and premature death, recent national and international guidelines for pharmacological COPD treatment consider them as "high-risk" patients.[3,4]

The hope of providing more effective protection against exacerbations through anti-inflammatory, non-steroidal alternatives has sparked major research efforts in the past few years.[5] This focused review will concisely highlight the pharmacological approaches based on anti-inflammatory biologics currently under investigation, emphasizing the few options more likely to be available in the Canadian market in 2025–2026. Two recent meta-analyses provide valuable information for those interested in further methodological details of the studies herein cited.[6,7]

A Snapshot of Inflammation in COPD

The "inflammasome" of COPD is surprisingly complex and varied. The key cells involved are neutrophils, macrophages, T lymphocytes, B lymphocytes, eosinophils, and innate lymphoid cells (ILCs). The predominance of specific cells over others likely reflects a mix of innate and adaptive immunological responses. Schematically, any type of airway-mediated inflammation requires:

- Triggers, including cigarette smoking, pollutants, oxidative stress, bacteria, and viruses;
- Proteins and peptides, known as "alarmins" (interleukin [IL]-33, IL-25, thymic stromal lymphopoietin [TLSP]) are released when there is cellular (epithelial) aggression or damage, (**Figure 1**)[8] to activate the immune system;
- Specific cells recruited by the alarmins which act as inflammatory mediators; and
- Chemical messengers ("cytokines") to orchestrate the multiple facets of the inflammatory response.

Neutrophilic/Macrophagic-dominant Inflammatory Response

In type 1 (T1) and T3 inflammation, T helper (Th) -1 and -17 cells and ILCs-1 and -3 activate macrophages and neutrophils, usually after microbial aggression.[1] The key cytokines involved include interferon (IFN)-γ, IL-6, IL-17, IL-21, IL-22, and tumour necrosis factor (TNF)-α. T1/T3 inflammation is the most common inflammatory response in COPD, occurring in 60-90% of patients.[9] Thus far, its pharmacological modulation has failed in clinical trials due to concerning safety signals. Efforts are ongoing to identify alternative immunological pathways, including inhibiting key receptors, targeting critical proteins and enzymes, modulating macrophages activity, and controlling oxidative stress and iron levels.[9]

Eosinophilic-dominant Inflammatory Response

When the alarmins recruit eosinophils, ILC-2, and, via dendritic cells, Th2, another set of cytokines are produced (IL-4, IL-5, and IL-13), characterizing T2 inflammation (**Figure 1**). IL-5 is important in recruiting eosinophils and directing their traffic to tissues. IL-4 and IL-13 bolster allergic and eosinophilic inflammation with consequent mucous hyper-secretion, barrier dysfunction, fibrosis, and tissue remodelling. Eosinophils, as well as IL-4, activate mast cells and basophils. A predominant T2 inflammatory response has been reported in 10-40% of stable COPD patients.[10] There is growing evidence that different signalling pathways are related to T2 inflammation in COPD versus asthma. This difference is likely related to differences in triggers, such as atopy and increased IgE-mediated mast cell activation in asthma versus cigarette smoke-related toxicity and oxidative, non-IgE-induced mast cell activation in COPD.[11] Despite the multitude of pathways involved, measuring the circulating blood eosinophil count (BEC) provides an acceptable estimate of the relative contribution of T2 inflammation in individual patients. Values ≥ 300 cells/μL are widely considered as indicative of dominant T2 inflammation.

Anti-inflammatory Biologics in COPD: What Has Not Worked (Yet?)

Alarmins Blockade

Anti-TSLP

Tezepelumab (Tezspire™, developed by AstraZeneca/Amgen) is a human monoclonal antibody that blocks the alarmin TSLP. In the COURSE trial, tezepelumab failed to significantly decrease the annualized rate of moderate or severe COPD exacerbations versus placebo in frequent exacerbators who were on triple therapy. Notably, a prespecified subgroup analysis showed a signal toward statistical significance in decreasing exacerbations in the subgroup showing a baseline BEC ≥ 150 cells/μL.[12] Currently, a small phase 2 **study** is evaluating the effect of tezepelumab on airway inflammation in patients with COPD receiving triple therapy with ≥ 1 exacerbation in the past 12 months (UPSTREAM-COPD).

Anti-IL-33

Itepekimab (REGN3500 or SAR440340, developed by Sanofi/Regeneron), a monoclonal antibody targeting interleukin (IL-33), failed to reduce the frequency of moderate to severe exacerbations compared to placebo in the entire study population.[13] Interestingly, a sub-analysis showed a signal toward improvement in former smokers; these results have prompted the current

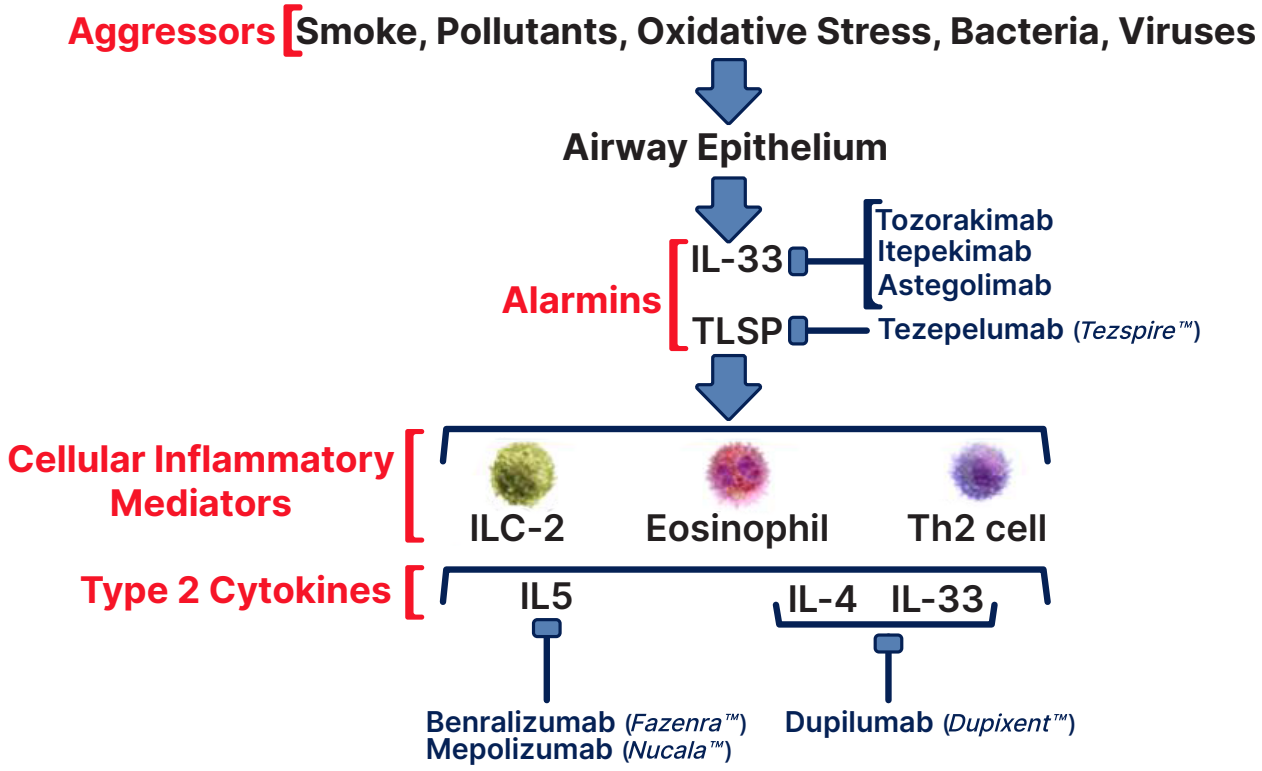

Figure 1. A simplified overview of the main pathways involved in the type 2 inflammatory response (T2) in patients with COPD; *courtesy of J. Alberto Neder, MD, PhD, DSc, FRCP(C), FERS.*

Abbreviations: COPD: chronic obstructive pulmonary disease, **IL:** interleukin, **TLSP:** thymic stromal lymphopoietin, **ILC:** innate lymphoid cell, **Th:** T helper.

AERIFY-1 and AERIFY-2 trials.[14] Tozorakimab (MEDI-3506, developed by AstraZeneca), another anti-IL-33 monoclonal antibody, did not improve lung function in COPD patients with chronic bronchitis on dual- or triple-inhaled maintenance therapy compared to placebo in the FRONTIER-4 study. However, it showed a numerical reduction in the risk of exacerbations, particularly in patients with ≥ 2 exacerbations in the previous year.[15] Four ongoing trials are looking at the potential effects of tozorakimab to reduce the burden of exacerbations compared to placebo (ClinicalTrials.gov; 2025). The results of the PROSPERO study are expected to be available by mid-2026. Astegolimab (developed by Genentech/Roche), a human IgG2 monoclonal antibody that binds to the IL-33 receptor ST-2, did not significantly reduce the exacerbation rate in patients with moderate-to-very severe COPD; however, it improved health status compared with placebo.[16] Three ongoing trials with similar endpoints are listed in ClinicalTrials.gov.

Anti-IL-5 Receptor α (IL-5Rα)

Benralizumab (Fasenra™, developed by AstraZeneca), a humanized monoclonal antibody targeting IL-5Rα, failed to reduce the annual rate of moderate or severe COPD exacerbations compared to placebo in two phase 3 trials (GALATHEA and TERRANOVA) involving patients with moderate-to-very severe COPD, most of whom had BEC levels ≥ 220/μL.[17] The results of the RESOLUTE trial with benralizumab in frequent exacerbators, who have BEC levels ≥ 300/μL at screening and a documented historical eosinophil count of ≥ 150/μL, are expected later in 2025.

Anti-inflammatory Biologics in COPD: What Has Worked (May 2025)

IL-4/IL-13 Receptor Blockade

Dupilumab (Dupixent™, developed by Sanofi/Regeneron) is a fully human monoclonal antibody that blocks the shared receptor component for IL-4 and IL-13. Two pivotal trials, NOTUS and BOREAS, showed a significant reduction (30-34%) in the annualized rate of moderate or severe exacerbations compared with placebo in both males and females. These patients experienced airflow obstruction, post-bronchodilator forced expiry volume in one second (FEV_1) of 30-70% predicted, symptoms of chronic productive cough for at least 3 months in the past year, chronic dyspnea (Modified Medical Research Council Dyspnea Scale [mMRC] ≥ 2), frequent exacerbations despite inhaled single- or multiple inhaled triple therapy, and evidence of T2 inflammation (BEC ≥ 300 cells/µL).[18,19] A pooled analysis of both trials confirmed and amplified these findings. Moreover, the time to the first severe exacerbation was significantly longer with dupilumab compared with placebo.[20] Subsequent analyses of these trials showed a positive effect on lung function,[21] regardless of the presence of emphysema.[22] Given the positive findings from NOTUS and BOREAS,[18,19] dupilumab was submitted for approval to Health Canada as an add-on maintenance treatment for adult patients with inadequately controlled COPD and an eosinophilic phenotype (T2 inflammation).

Anti-IL-5

Initial negative results vis-à-vis exacerbation burden were reported with the anti-IL-5 mepolizumab (Nucala™, developed by GlaxoSmithKline [GSK]) in the METREO and METREX trials.[23] Of note, the manufacturer **announced** on September 6th, 2024 that the primary endpoint of a significant reduction in the annualized rate of moderate/severe exacerbations "has been reached with mepolizumab versus placebo with data up to two years" in the MATINEE study. This randomized controlled trial enrolled frequent exacerbators despite triple therapy, with BEC levels ≥ 300/µL.[24] Based on these results, the manufacturer **announced** on February 26th, 2025, that a Supplementary New Drug Submission has been accepted by Health Canada to expand the use of mepolizumab to patients with COPD showing an eosinophilic phenotype. The positive MATINEE results were eventually published on April 30th, 2025: mepolizumab led to 21% lower annualized rate of moderate or severe exacerbations when added to background triple inhaled therapy among frequent exacerbators with COPD and an eosinophilic phenotype.[25]

Selecting the Right COPD Patient at the Right Time for Biologic Therapy

A potential practical step-by-step guide for initiating biologic treatment for COPD is outlined in **Figure 2**. It is paramount to ensure that the candidate has received the optimal prophylaxis for COPD exacerbations including at least inhaled triple therapy.[3,4] The most reasonable criteria for discontinuing treatment is the lack of effect, i.e., similar annual exacerbation rates after at least 6 months compared to pre-treatment. Supporting evidence for treatment failure includes worsening symptoms (sputum production and dyspnea) and a progressive decrement in lung function (FEV_1) beyond the expected age-adjusted rate (25-30 mL/year, up to 50-60 mL/year in individuals older than 70 years). The frequency of side effects was generally similar to that of placebo in all trials with dupilumab[18,19] and mepolizumab.[25] Similar to other biologics, a healthcare professional should administer the first or subsequent doses in a clinical setting. Given the complexities involved in selecting and following these patients, a respirologist should coordinate the patient's treatment.

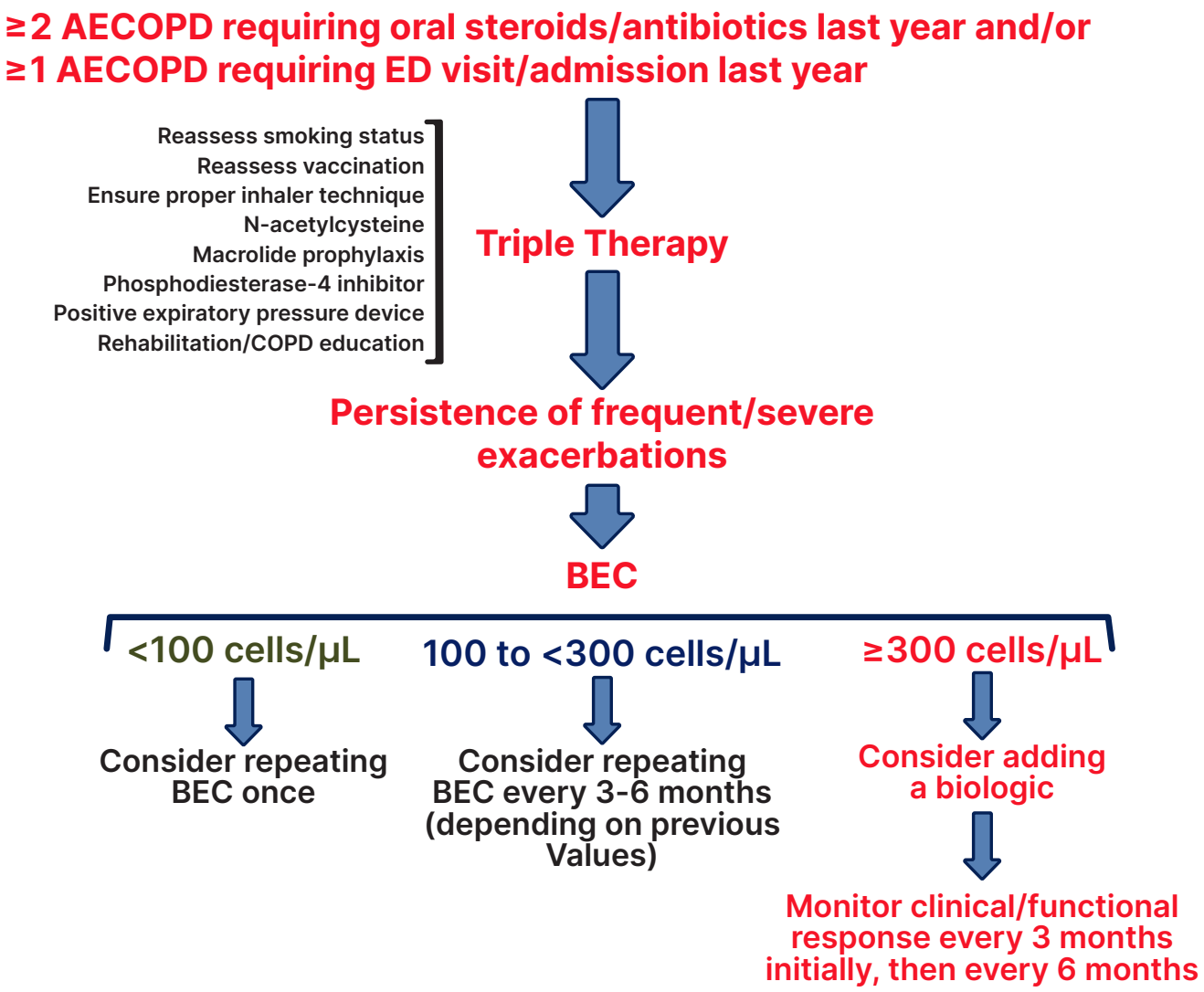

Figure 2. A pragmatic algorithm for selecting COPD patients most likely to derive clinical and functional benefits from IL-4/IL-13 receptor blockade (injectable dupilumab); *courtesy of J. Alberto Neder, MD, PhD, DSc, FRCP(C), FERS.*

Abbreviations: AE: acute exacerbation, **COPD:** chronic obstructive pulmonary disease, **coED:** Emergency Department, **BEC:** blood eosinophil counts, **SC:** subcutaneous.

Points to Ponder:

Some pertinent questions on the use of biologics in COPD remain unanswered, requiring further research:

- Is a single BEC measurement, either above or below 300 cells/μL, enough to rule in or out T2 inflammation in COPD?
- If not, is it useful to track BEC levels over time?
- If so, how often should measurements be taken? Would the frequency of BEC measurements vary according to previous levels, e.g., every 3-6 months in frequent exacerbators with borderline levels (200 to <300 cells/μL), or yearly in those with values between 100-200 cells/μL?
- How long should a persistent exacerbator be on maximal prophylactic treatment (**Figure 2**) before a biologic is considered?
- Assuming multiple biologics are eventually approved for COPD treatment, would the coexistence of asthma impact the selection?
- Could biologics improve the efficacy of treating eosinophilic exacerbations in COPD ? A small, two-centre study suggests this might be the case; however, 68% of the patients enrolled in this study had asthma or asthma-COPD overlap.[26] In any case, this question warrants investigation in a large randomized controlled trial with "pure" COPD patients.
- Should we consider BEC as a continuous variable rather than adhering to an absolute threshold for indicating biologics in COPD? It is likely that selected patients with values in the "grey zone" (100-300 cells/μL) would benefit from a biologic. We need to improve our tools to better identify these patients, likely using a combination of clinical, laboratory (biomarkers), and, potentially, imaging data.

Conclusions

Treatment of COPD has evolved markedly over the past few decades. The use of biologics opens a clear perspective for a more personalized therapeutic approach based on clinical features (phenotypes) and biomarkers (endotypes). Currently, addressing T2 inflammation has been more rewarding than anti-T1/T3 treatments. The available data are reassuring, showing no concerning safety signals in any of the tested medications.[6,7] Given the large heterogeneity in study phases, sample sizes, and inclusion criteria vis-à-vis BEC counts and other biomarkers, it is still too early to determine whether there will ever be a "better" biologic for T2 inflammation in COPD. Considering the heterogeneity of the T2 Response (**Figure 1**) and the disease itself, it is more realistic to expect that different phenotypes and/or endotypes will benefit from different biologics.[27] The potential for dupilumab[18,19] and mepolizumab[25] as the first biologics approved for treating inadequately controlled patients with a history of frequent exacerbations despite inhaled triple therapy is eagerly anticipated by all involved in the care of COPD. With rapid progress in the field, it is likely that several other products will be approved for use in the coming years.

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