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Editorial Board

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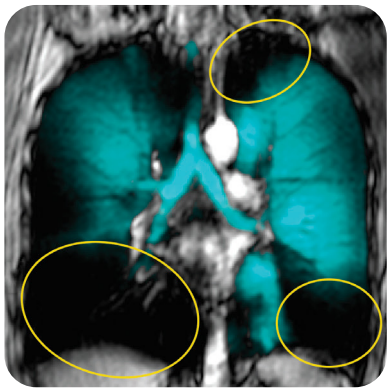

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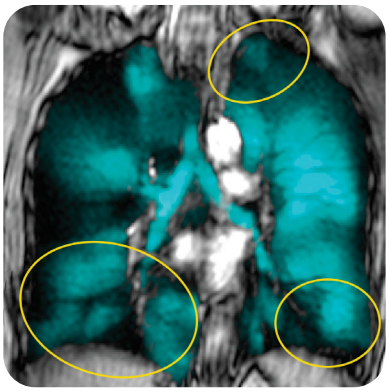
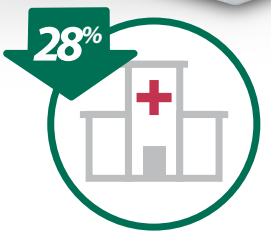


Teal colour and intensity show areas with gas distribution. Yellow circles represent areas of greatest change **after 3–4 weeks of *Aerobika***® device use.[4]



reduction in COPD exacerbations at 30 days[5]

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1 GOLD 2025 Report. **2** Suggett, J. et al. CHEST 2017. **3** Van Fleet H, *et al*. Respiratory Care 2017;62(4):451-458. **4** Svenningsen S, et al. J COPD 2016;13(1):66–74. **5** Burudpakdee C, et al. Pulm Ther 2017;3(1):163-171.
6 Adapted from Svenningsen S, et al. J COPD 2016;13(1):66-74.

About the Authors

Tsu-Yu Unice Chang, BSc, MD, FRCPC

Dr. Tsu-Yu Unice Chang completed her medical school and core internal medicine training at the University of Manitoba before completing her medical oncology residency at the University of Ottawa. She is currently a clinical fellow at the University of Ottawa with a focus on lung cancer and medical education.

Affiliations: University of Ottawa, Department of Medicine, Ottawa, Ontario, Canada

Paul Wheatley-Price, BSc, MBChB, FRCP (UK), MD

Dr. Paul Wheatley-Price is a medical oncologist at The Ottawa Hospital Cancer Centre, specializing thoracic malignancies and carcinoma of unknown primary. He is the lung cancer disease site lead in medical oncology, and also the Program Director for the University of Ottawa Residency Training Program. He served as President of Lung Cancer Canada from 2016–2021, and remains a Board member and active lung cancer advocate.

Affiliations: University of Ottawa, Department of Medicine, Ottawa, Ontario, Canada
Ottawa Hospital Research Institute, Ottawa, Ontario, Canada

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Current Immunotherapies for Lung Cancer: A Review for Respirologists

Tsu-Yu Unice Chang, MD
Paul Wheatley-Price, MD

Introduction

Due to revolutionary advancements in treatment, lung cancer has had the largest improvement in mortality of all cancers over the last two decades. Despite this, it remains the type with the highest incidence and mortality of all cancers in Canada, and globally it has the second highest incidence and highest mortality.[1,2]

An important mechanism for cancer cell survival, and one of the hallmarks of cancer, is evasion of destruction by immune cells.[3] Immunotherapy is a class of systemic therapy aimed at activating the cytotoxic activity of immune cells and is one of the major drivers behind the improvement in survival of patients with lung cancer (along with targeted therapies, which will not be covered in this review). Immune checkpoint inhibitors (ICIs) are monoclonal antibodies that disrupt immunosuppressive signaling and result in increased activity of cytotoxic T cells. This article discusses the currently available ICIs and their indications in the treatment of lung cancer, immune-related toxicities and important contraindications to treatment, and a respirology-focused overview of the management of toxicities. This is not a comprehensive review of immunotherapy trials in lung cancer.

How Does Immunotherapy Work?

PD-1/PD-L1 inhibitors

The cell-killing activity of immune cells in the body is carefully modulated to maintain the ability to destroy foreign substances while controlling excessive inflammation and retaining self-tolerance through various "immune checkpoints". Some cancers take advantage of these tolerance mechanisms to evade immune destruction.[4] Programmed cell death protein ligand 1 (PD-L1) is a cell surface protein variably expressed on cancer cells. When it binds to programmed cell death protein 1 (PD-1) on T cells, it inhibits its cytotoxicity towards cancer cells. ICI block the binding of PD-1 to PD-L1, essentially 'releasing the brakes' and allowing T cell killing of the tumour cell. Upregulation of PD-L1 is common in lung cancer and can be reported as a tumor proportion score (TPS) from <1% to 100% via commercially available immunohistochemistry assays.[5] While not a perfect biomarker, higher expression generally predicts better response to immunotherapy. Expression levels ≥50% are considered 'high', levels from 1–49% are 'intermediate', and <1% is low or negative. In tumors with a high PD-L1 expression (≥50%), PD-1/PD-L1 inhibitors can be used as monotherapy.[6-8]

There are several monoclonal antibodies targeting PD-1 or PD-L1 available for cancer treatment, and those with Health Canada-approved indications are summarized in **Table 1**. Where different agents were tested in the same setting, many showed comparable benefit and toxicity profiles. Initially starting as second-line treatment for metastatic non-small cell lung cancer (NSCLC), these have now also shown efficacy as first-line therapy, adjuvant and neoadjuvant therapy for NSCLC, in both limited stage and extensive stage small cell lung cancer (SCLC), and in malignant pleural mesothelioma (MPM).

CTLA-4 Inhibitors

Cytotoxic T-lymphocyte antigen 4 (CTLA-4) is another checkpoint inhibitor of T cell activation and plays an important role in preventing immune reactions to self-antigens.[4] An early trial in melanoma that compared CTLA-4 inhibition to PD-1 inhibition versus dual immunotherapy showed that the CTLA-4 monotherapy resulted in significantly worse survival than PD-1 monotherapy, with combination immunotherapy superior to single agent.[9] Subsequently, CTLA-4 inhibitors have

Drug	Brand name	Class	Health Canada-approved indication(s)
pembrolizumab	Keytruda	PD-1	**1st line:** advanced/metastatic NSCLC
			2nd line: advanced/metastatic NSCLC
			Adjuvant: Stage II-III NSCLC after surgical resection
durvalumab	Imfinzi	PD-L1	**Adjuvant:** unresectable Stage III NSCLC, after chemoradiation
			1st line: extensive stage small cell lung cancer, combined with platinum-based chemotherapy
			Adjuvant: limited stage small cell lung cancer, after platinum-based chemoradiation
atezolizumab	Tecentriq	PD-L1	**1st line:** extensive stage small cell lung cancer, combined with platinum-based chemotherapy
			Adjuvant: NSCLC with PD-L1 expression >50%, after surgical resection and followed by platinum-based chemotherapy
			1st line: advanced/metastatic NSCLC
			2nd line: advanced/metastatic NSCLC
nivolumab	Opdivo	PD-1	**2nd line:** advanced/metastatic NSCLC
			1st line: advanced/metastatic NSCLC, in combination with ipilimumab for PD-L1 expression >1%
			1st line: advanced/metastatic NSCLC, in combination with ipilimumab and two cycles of platinum-based chemotherapy
			Neoadjuvant: resectable NSCLC >4cm or node-positive, in combination with platinum-based chemotherapy
cemiplimab	Libtayo	PD-1	**1st line:** advanced/metastatic NSCLC
ipilimumab	Yervoy	CTLA-4	**1st line:** advanced/metastatic NSCLC, in combination with nivolumab for PD-L1 expression >1%
			1st line: advanced/metastatic NSCLC, in combination with nivolumab and two cycles of platinum-based chemotherapy

Table 1. Immune checkpoint inhibitors with Health Canada-approved indications in the treatment of lung cancer as of October 2024; *courtesy of Tsu-Yu Unice Chang, BSc, MD, FRCPC and Paul Wheatley-Price, BSc, MBChB, FRCP (UK), MD*.

Abbreviations: CTLA-4: cytotoxic T lymphocyte-associated protein 4, **NSCLC:** non-small cell lung cancer, **PD-1:** programmed cell death protein 1, **PD-L1**: programmed cell death ligand 1.

only been tested in combination with PD-1/PD-L1 blockade and are no longer in use as single agents.

There is currently one CTLA-4 inhibitor with a Health Canada-approved indication in lung cancer, ipilimumab, given in combination with nivolumab and chemotherapy. This regimen is less commonly used in lung cancer due to the higher risk of immune-related toxicities with dual immunotherapy. However, it represents a good option in those with low tumoral PD-L1 expression, where single agent anti-PD-1/PD-L1 treatment has much lower response rates.[10] Dual immunotherapy is also used in MPM, with particular efficacy in the most aggressive sarcomatoid subtype.[11]

Administration

ICI are typically administered intravenously (IV) as a 30–60-minute infusion, every 2–6 weeks, depending on the specific regimen. Early trials of immunotherapy used weight-based dosing; however, ICIs show similar effects at a large range of concentrations. As both efficacy and risk of toxicity are largely dose-independent, modern clinical trials have switched to flat dosing for ease of administration. Subcutaneous formulations are in development to decrease administration time and increase patient convenience, and are likely to be available within the next couple of years.[12] Infusion reactions are uncommon, and in contrast to chemotherapy, no supportive medications (steroids, anti-emetics) are routinely needed.

Efficacy

Immunotherapy has shown wide-ranging benefits across multiple settings, improving cure rates in early-stage NSCLC and SCLC and prolonging survival in metastatic NSCLC, SCLC, and MPM. Treatment in NSCLC is sometimes stratified by PD-L1 expression, whereas in SCLC, immunotherapy is combined with chemotherapy in all patients. In MPM, benefit of immunotherapy relative to chemotherapy is predicted by non-epithelioid histology rather than PD-L1 expression. Selected survival data from practice-changing trials are included in **Figure 1**.

An encouraging effect of immunotherapy is that, even in the metastatic setting, a significant minority of patients experience long-term disease control even after discontinuation of treatment, unlike chemotherapy and targeted agents, where the expected course is to eventually develop resistant disease.

It should be noted that PD-L1 is not a perfect predictor of response to immunotherapy and special considerations exist in non-smokers, who have a much lower response even with high PD-L1 expression.[13] These patients should be considered for combination chemoimmunotherapy rather than immunotherapy alone. Patients with certain driver mutations associated with non-smoking status, such as epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK), are known to have virtually no response and have been excluded from almost all major immunotherapy trials. These patients should not be treated with immunotherapy given the same risk of toxicities, lack of treatment benefit, and the availability of very effective targeted therapies as an alternative.

Immune Toxicities

While ICIs are well tolerated in general, and serious adverse events are less common than with chemotherapy, immune-related adverse events (irAEs) can occur. Use of these drugs is associated with a wide variety of autoimmune reactions that can affect any organ system in the body. Common irAEs include rash, colitis, and hypothyroidism (sometimes preceded by hyperthyroidism). Furthermore, these therapies can also cause other permanent endocrinopathies (e.g. adrenal insufficiency, Type 1 diabetes) as well as life-threatening organ inflammation (e.g. pneumonitis, myocarditis)[14]

Patients with pre-existing autoimmune conditions such as inflammatory bowel disease and rheumatoid arthritis have been excluded from clinical trials, and retrospective data show these patients are at risk of a flare of their autoimmune condition, which can affect as high as 41% of patients with inflammatory bowel disease.[15] Therefore, this therapy may be contraindicated in these patients, but depending on the other therapeutic options available and risk/benefit ratio, can still be considered with careful counselling.

Two conditions that should be considered absolute contraindications to immunotherapy are pre-existing interstitial lung disease (ILD) and thymoma. Radiologic evidence of ILD is associated with six-fold odds of developing ICI-induced pneumonitis, which has a 25–30% mortality rate.[16,17] Immunotherapy in thymomas is associated with serious or life-threatening toxicity at a rate upwards of 60–70%, with neuromuscular or muscular complications such as myasthenia gravis being particularly prominent.[18]

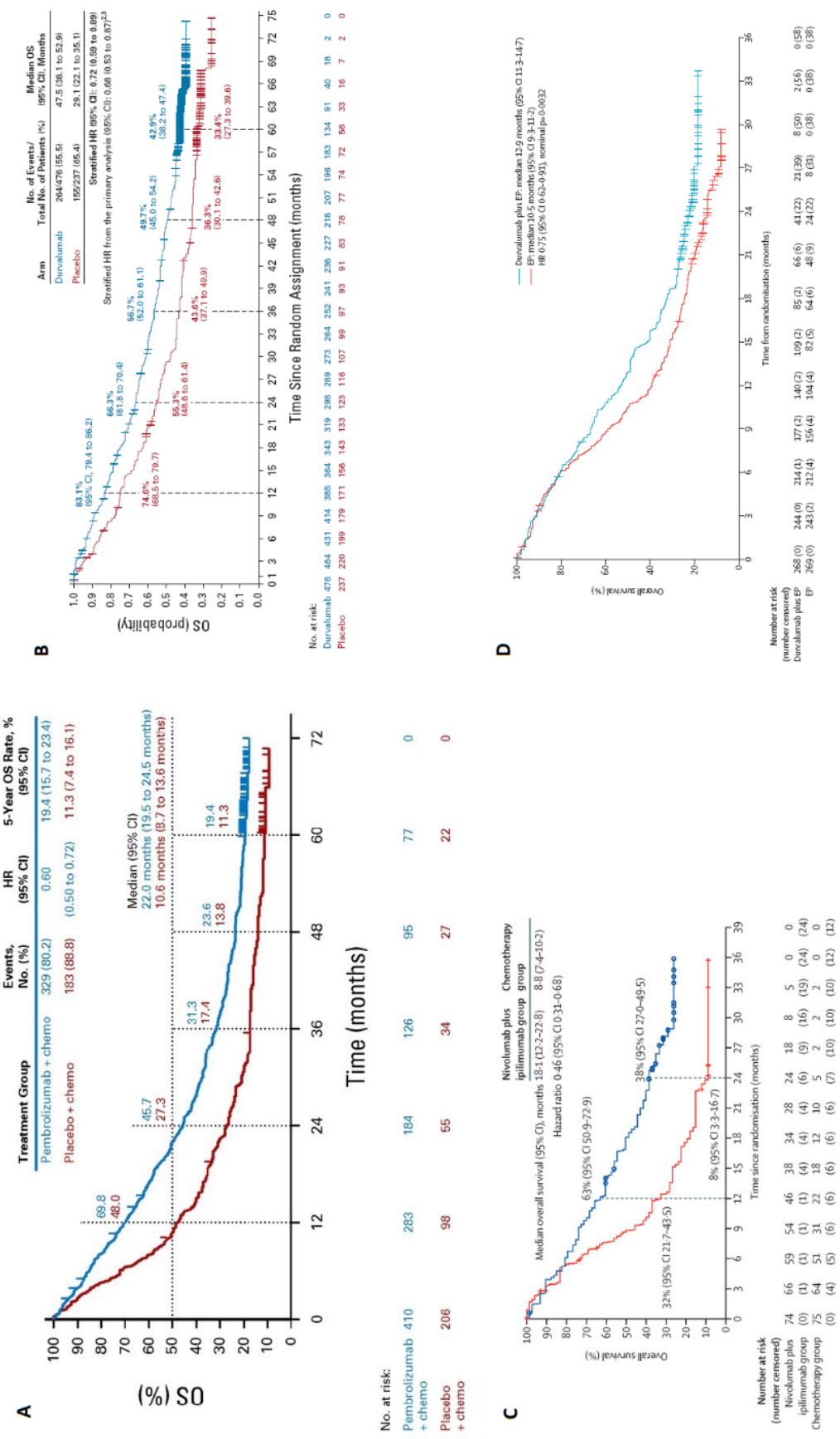

Figure 1. Kaplan-Meier survival curves in several practice-changing clinical trials in lung cancer. **A:** Overall survival in the intention-to-treat population from KEYNOTE-189, metastatic non-small cell lung cancer treated with first-line chemotherapy plus pembrolizumab compared to chemotherapy alone.[13] **B:** Overall survival comparing first-line chemotherapy plus durvalumab versus chemotherapy alone in extensive stage small cell lung cancer from the CASPIAN trial.[21] **C:** Overall survival comparing first-line dual immunotherapy with nivolumab and ipilimumab versus chemotherapy in pleural mesothelioma with non-epithelioid histology from CHECKMATE 743.11 **D:** Overall survival in patients treated with adjuvant durvalumab versus placebo after curative intent chemoradiation for locally advanced, unresectable non-small cell lung cancer from the PACIFIC trial.[22]

Management of Immune Toxicities

irAEs are graded according to the Common Terminology Criteria for Adverse Events (CTCAE), in which Grade 1 is mild or asymptomatic, Grade 2 is moderate and warranting local or limited intervention or affecting age appropriate instrumental activities of daily living, Grade 3 is severe and disabling or warranting hospitalization, Grade 4 is life-threatening and warranting urgent intervention, and Grade 5 is causing death.[19]

In general, Grade 1 irAEs can be monitored while continuing immunotherapy. Grade 2 irAEs warrant holding immunotherapy until symptoms improve to Grade 1 or less, with consideration given to initiation of oral prednisone at a dose of 0.5–1 milligrams per kilogram of body weight, tapered over 4–6 weeks. In the case of steroid administration, immunotherapy should be held until it is tapered to a daily prednisone equivalent of ≤10 mg without flare-up of symptoms. Grade 3–4 irAEs warrant hospitalization, with IV methylprednisolone started at a dose of 1–2 mg/kg, switched to oral prednisone and tapered over 6 weeks once improving. Patients who do not improve within 48-72 hours or who experience an inability to taper off prednisone without flare-up should have secondary immunosuppression initiated with other agents, the choice of which is organ dependent and consultation with the relevant organ system specialist and reference to a guideline such as the American Society of Clinical Oncology (ASCO) guideline on irAE is recommended.[20] In general, patients with Grade 3 toxicities can be rechallenged with immunotherapy once the irAEs are resolved to Grade 1 on ≤10 mg of daily prednisone, but those with Grade 4 should permanently discontinue treatment.

Key exceptions exist to the general management strategies. Due to the high risk of mortality, even Grade 1 myocarditis should be managed with permanent discontinuation of the ICI and initiation of steroids. For pneumonitis, consideration should be given to holding the ICI even for Grade 1 incidental radiological findings and it should be permanently discontinued for Grade 3 events (requiring oxygen supplementation). Conversely, ICI-induced endocrinopathies are permanent regardless of any treatment and the ICI can be continued with appropriate hormone replacement.

Diagnosis of ICI-induced Pneumonitis

ICI-induced pneumonitis can be difficult to definitively diagnose in patients with lung cancer, as symptoms such as shortness of breath, cough, and hypoxia can also be caused by pneumonia, chronic obstructive pulmonary disease (COPD), or complications of cancer progression, such as lymphangitic carcinomatosis. A variety of appearances may be observed by computed tomography (CT), including ground-glass opacities, organizing pneumonia, and various forms of ILD.[17]

Initial management of such patients usually involves initiation of treatment for all possible causes, including antibiotics for possible pneumonia, inhaler therapy for COPD, and steroids for pneumonitis. It is important that steroids are not delayed while awaiting diagnostic clarification, as this is associated with increased morbidity and mortality.

Respirologists may be consulted to aid in diagnostic clarification, with bronchoscopy and bronchoalveolar lavage being helpful to evaluate for an infectious cause.

Conclusions

ICIs are a class of anti-cancer therapies that have revolutionized the treatment of lung cancer and many other cancers, such as melanoma, renal cell carcinoma, head and neck cancers, triple-negative breast cancer, and certain subtypes of colorectal cancer. These drugs are generally well tolerated but come with the potential for a wide range of autoimmune toxicities. Early identification of irAEs and prompt treatment with immunosuppressive agents is key for minimizing morbidity and mortality. Pneumonitis is a relatively rare complication of immunotherapy but is associated with a higher mortality rate and respirologists may be consulted for help with management and diagnostic clarification in these cases.

Correspondence

Paul Wheatley-Price, BSc, MBChB, FRCP (UK), MD
Email: pwheatleyprice@toh.ca

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About the Author

J. Alberto Neder, MD, PhD, DSc, FRCP(C), FERS

Dr. J. Alberto Neder, Professor of Respiratory Medicine at Queen's University, specializes in cardiopulmonary interactions, exertional dyspnea, and clinical respiratory physiology. He has authored over 300 peer-reviewed papers and numerous books and chapters on respiratory and exercise physiology, pulmonary rehabilitation, and integrated care for chronic respiratory diseases. He serves as Medical Director of Kingston General Hospital's Respiratory Investigation Unit, Hotel Dieu Hospital's Pulmonary Function Tests Laboratory, and Providence Care Hospital's Pulmonary Rehabilitation Program in Kingston, ON. His clinical and teaching interests include chronic obstructive pulmonary disease (COPD), COPD-heart failure overlap, pulmonary rehabilitation, pulmonary vascular disease, lung function, and cardiopulmonary exercise tests.

Affiliations: Respiratory Investigation Unit, Division of Respirology and Sleep Medicine, Department of Medicine, Queen's University, Kingston, Ontario, Canada

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

J. Alberto Neder, MD, PhD, DSc, FRCP(C), FERS

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

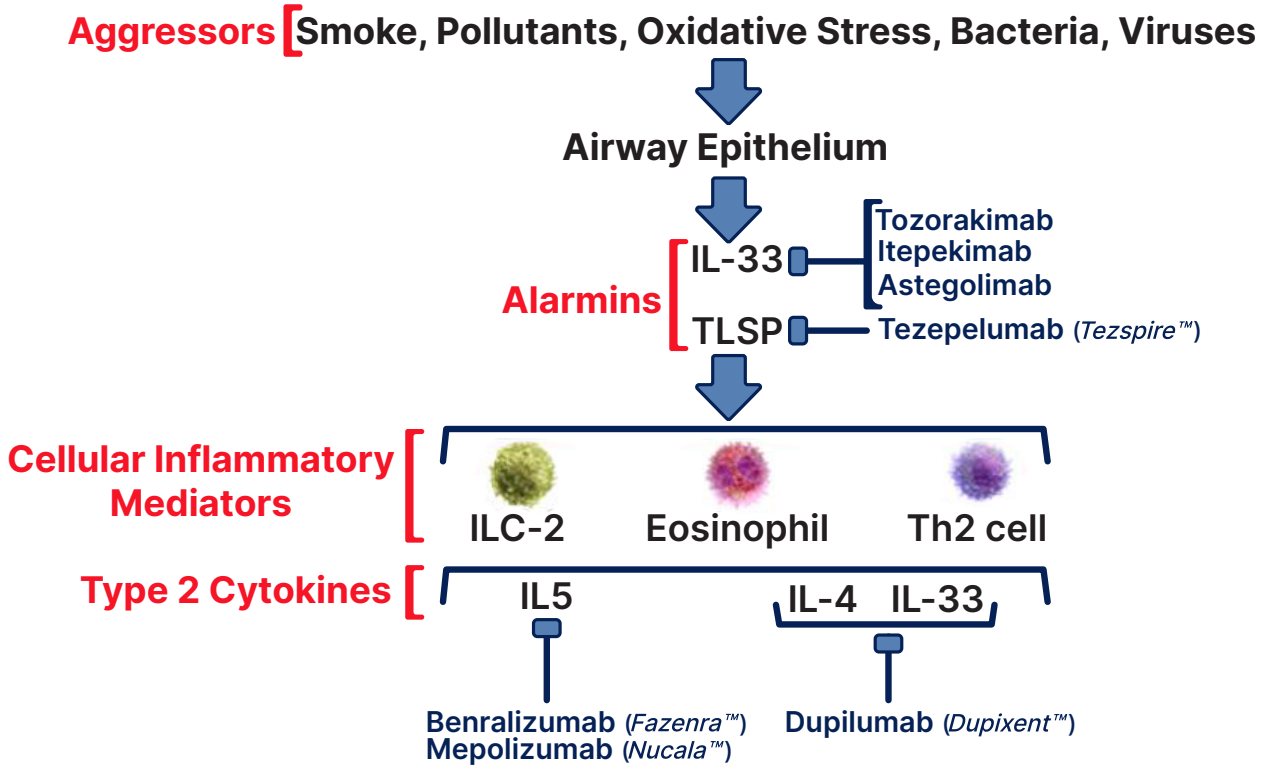

Figure 1. A simplified overview of the main pathways involved in the type 2 inflammatory response (T2) in patients with COPD; *courtesy of J. Alberto Neder, MD, PhD, DSc, FRCP(C), FERS.*

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.

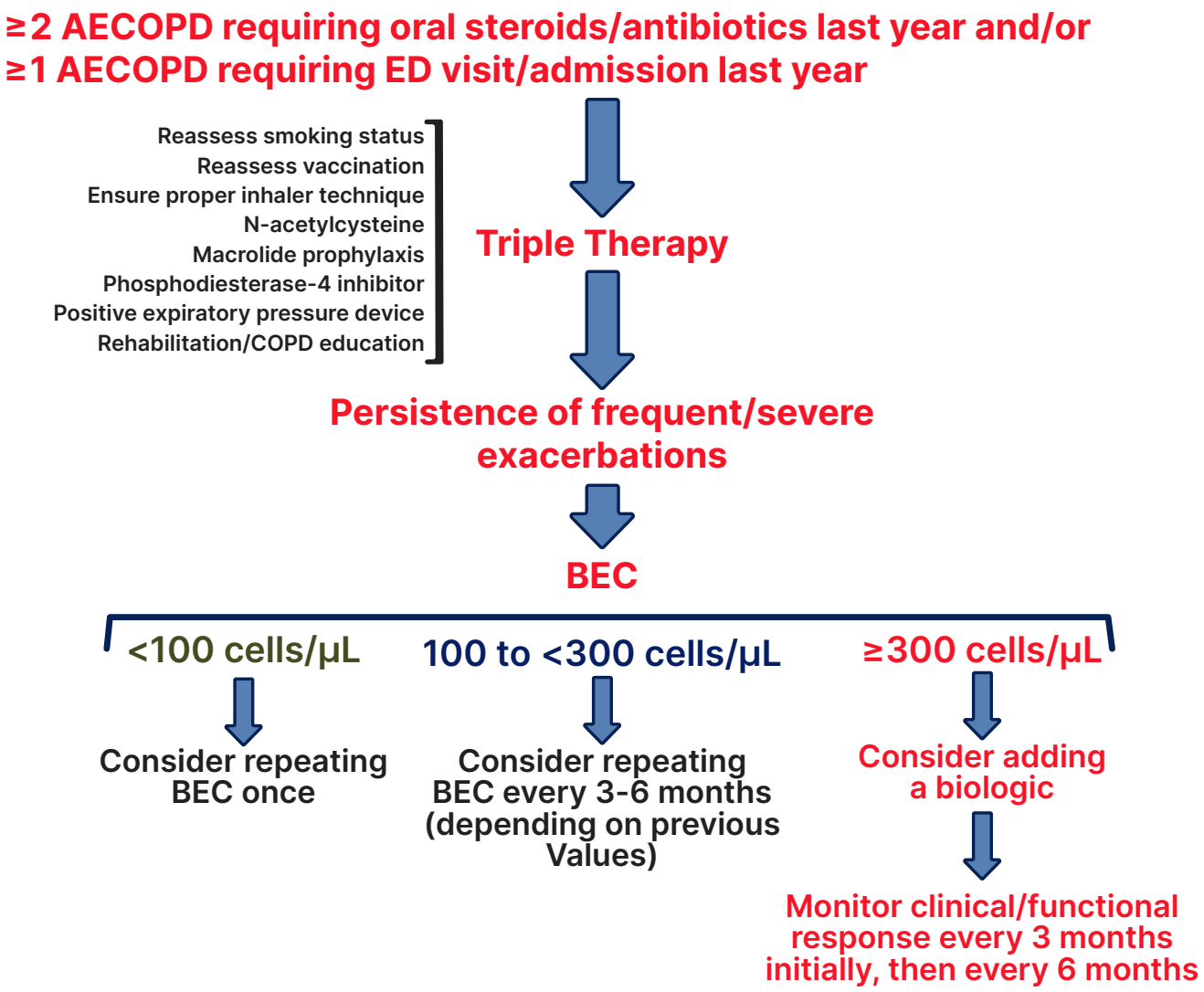

Figure 2. A pragmatic algorithm for selecting COPD patients most likely to derive clinical and functional benefits from IL-4/IL-13 receptor blockade (injectable dupilumab); *courtesy of J. Alberto Neder, MD, PhD, DSc, FRCP(C), FERS.*

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.

Correspondence

J. Alberto Neder, MD, PhD, DSc, FRCP(C), FERS
Email: alberto.neder@queensu.ca

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About the Authors

Jason K. Lee, MD, FRCPC, FAAAAI, FACAAI

Dr. Jason Lee is a practicing physician specializing in immunotherapy treatment of allergic diseases, including allergic asthma, at Toronto Allergists in Toronto, ON, Canada, where he is also clinical director and managing partner. In addition, he is CEO of Evidence Based Medical Educator Inc in Toronto and the founder and chair of Urticaria Canada, an advocacy and patient support organization whose goal is to educate patients and health care professionals about chronic urticaria. Dr. Lee earned a Doctor of Medicine degree from the Faculty of Medicine at the University of Toronto. He subsequently received fellowship training in internal medicine at the University of British Columbia in Vancouver, Canada, and in clinical immunology and allergy at the University of Toronto. Dr. Lee's research interests include asthma, urticaria, nasal polyps, chronic cough, and atopic dermatitis. Among his accomplishments is working on the national consensus guidelines on immunoglobulin replacement therapy for secondary immune deficiencies and co-authorship of the original first paper on the use of dupilumab for chronic spontaneous urticaria in patients who had failed to respond to omalizumab. Dr. Lee has served as section head of asthma at the Canadian Society of Allergy and Clinical Immunology and is currently a member of the Biologics and Therapeutics Committee of the American College of Allergy, Asthma, and Immunology.

Affiliations: Toronto Allergists, Toronto Allergy and Asthma Clinic, Evidence Based Medical Educator Inc, Toronto, ON, Canada

Christian Pagnoux, MD, MSc, MPH

Dr. Pagnoux trained in internal medicine and clinical immunology in Paris (France). Between 2002 and 2010, he worked in Paris and has served as vice-president of the French Vasculitis study group. He moved to Toronto (Canada) in 2010 and was appointed in the Division of rheumatology at the Mount Sinai Hospital. He joined the steering committee of the North American Vasculitis Clinical Research Consortium (VCRC), and founded CanVasc, the Canadian network for research in vasculitis. He has been involved in many important studies in vasculitis, led by the French, European or North-American groups, has written or co-authored more than 300 peer-reviewed publications and several textbook chapters on vasculitis.

Affiliations: Vasculitis Clinic, Mount Sinai Hospital, Department of Medicine, Division of Rheumatology, University of Toronto, Toronto, Ontario, Canada

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Advances in the Therapy of Eosinophilic Granulomatosis with Polyangiitis (EGPA) in 2025

Jason K. Lee, MD
Christian Pagnoux, MD

Eosinophilic granulomatosis with polyangiitis (EGPA) is a rare systemic vasculitis affecting small to medium-sized vessels, characterized by asthma, eosinophilia, and inflammation. Recent advances in the understanding of EGPA pathogenesis have facilitated the development of targeted therapies, particularly biologics, aimed at improving disease control and reducing treatment-associated toxicity. This review discusses the current therapeutic landscape for EGPA in 2025, highlighting key clinical trials, real-world data, and future directions.

Introduction

Eosinophilic granulomatosis with polyangiitis (EGPA), formerly known as Churg-Strauss syndrome, is a multisystem disorder with a heterogeneous clinical presentation, typically affecting the respiratory system (all patients), peripheral nerves (up to 60% of patients), and skin (40–60% of patients). Cardiac involvement is rarer (up to 25% of patients) but carries a poor prognostic value. Although EGPA is one of the 3 antineutrophil cytoplasm antibodies (ANCA)-associated vasculitides (along with granulomatosis with polyangiitis and microscopic polyangiitis), only 30–40% of patients with EGPA are ANCA positive (mostly with MPO-ANCA).[1]

The disease's rarity (annual incidence of 1–2 per million in North America or Europe) complicates the development of standardized treatments. Historically, glucocorticoids (GC) and conventional immunosuppressants such as cyclophosphamide and azathioprine formed the cornerstone of treatment, selected based on disease severity.[2,3] However, the limited efficacy and significant morbidity associated with these therapies have necessitated the exploration of other, safer and more targeted approaches.[4]

Recent insights into EGPA's immunopathology, particularly the roles of interleukin-5 (IL5) and eosinophils, in parallel with advancing research on eosinophilic asthma, have paved the way for biologics such as mepolizumab and benralizumab. Rituximab has emerged over the past 20 years as a major treatment for granulomatosis with polyangiitis and microscopic polyangiitis, and it has more recently been investigated for use in EGPA. This article reviews the current evidence on these therapies and their integration into clinical practice.

Pathogenesis and Cytokine Driven Therapeutics

1. ***Mepolizumab:*** Mepolizumab, a humanized anti-IL5 monoclonal antibody, was the first biologic approved for EGPA. The pivotal MIRRA trial demonstrated that mepolizumab (300 mg subcutaneously, every 4 weeks) significantly increased remission rates compared to placebo (32% vs 3%, respectively), and reduced GC use and dependence.[4] Follow-up studies have confirmed its efficacy in maintaining long-term remission, especially in ANCA-negative patients.[5-8] However, its efficacy for acute, more severe manifestations of EGPA, such as cardiomyopathy or mononeuritis multiplex, remains unknown.

2. ***Benralizumab:*** Benralizumab, which targets the IL5 receptor α, blocks the IL5 pathway, and induces eosinophil apoptosis through antibody-dependent cellular cytotoxicity. It has recently been approved by the FDA for the treatment of EGPA. A few trials showed good results in patients with refractory or GC-dependent EGPA.[9] The recent results of the head-to-head comparative MANDARA trial showed similar efficacy in the rate of remission at week 52 for benralizumab (30 mg subcutaneously, every 4 weeks) or mepolizumab (59% vs 56%, respectively). In addition, slightly more EGPA patients achieved a GC-free remission at week 52 with benralizumab (a secondary endpoint; 41% vs 26% with mepolizumab).
3. ***Dupilumab:*** Dupilumab, an anti-IL4 and IL13 monoclonal antibody, has gained attention for EGPA patients based on its efficacy in treating eosinophilic asthma and atopic comorbidities.[10] Early-phase trials suggest that dupilumab may reduce asthma exacerbations and eosinophil tissue infiltration, although its vasculitis-modifying effects remain under investigation.

Rituximab, Conventional Therapies and Their Role in 2025

Despite the rise of the latter anti-IL5 (and other anticytokine) biologics, conventional therapies remain relevant for relapsing, severe, and/or organ-threatening disease. To date, treatment choices are mostly based on disease severity and patient clinical characteristics (**Figure 1**). ANCA-positive and ANCA-negative patients are treated similarly, and independently of the precise level of their eosinophil count at the time of a flare or their genetic background. Patients with cardiac, severe renal, gastro-intestinal, and/or central nervous system involvement(s) require the most aggressive treatment. Patients with progressing and/or severe neuropathic, ocular, or gangrenous skin involvement should also receive intensive treatment. In 2025, intense or aggressive approaches remain based on high-dose GC and immunosuppressants, mostly cyclophosphamide.[11] Rituximab can be considered as an alternative to cyclophosphamide in some cases, but there is still limited data to confirm its equivalence in all situations. Patients with less severe EGPA can initially be treated with GC alone. However, the early addition of mepolizumab or benralizumab can be considered, because up to 80% of these patients will likely develop GC-dependent asthma or sinonasal polyposis.

The long-term use of cyclophosphamide is limited by its significant adverse effects, including infertility and secondary malignancies.[12] Methotrexate and azathioprine are widely used as GC-sparing agents in general, and for maintenance therapy in EGPA, following cyclophosphamide-based induction in severe cases.[13] Although they are safer than cyclophosphamide in general, their efficacy remains limited, and neither methotrexate, azathioprine nor mycophenolate mofetil have been rigorously studied in EGPA. Only 1 randomized controlled trial was conducted with azathioprine for induction in non-severe EGPA, comparing it to a placebo and in combination with GC. The trial showed no added benefit from azathioprine.

Rituximab, primarily used in ANCA-associated vasculitis, has shown promise in small EGPA cohorts, particularly in ANCA-positive patients.[14] A recent trial (REOVAS) showed that rituximab-based induction is not superior to GC alone for non-severe EGPA, nor to GC and cyclophosphamide for severe EGPA. While rituximab may be a probable alternative to cyclophosphamide for severe EGPA, this has not been fully demonstrated. In addition, the appropriate course of action after remission is achieved with rituximab-based regimens remains uncertain. Repeat rituximab infusions (every 6 months) are now the standard of care for maintenance in granulomatosis with polyangiitis and microscopic polyangiitis; however, this approach has not been proven effective for EGPA. A study is ongoing (in France) to compare azathioprine and rituximab in patients with EGPA who have achieved remission with GC and cyclophosphamide (or rituximab, for some). Mepolizumab for maintenance after rituximab-based induction has also been investigated in small case series.

Glucocorticoid-Sparing Strategies

Previous studies, conducted prior to the era of biologics, have shown that up to 80% of patients with EGPA can achieve remission of the "vasculitic", non-asthma, non-ear nose throat (ENT) manifestations.[15] However, these patients will remain GC-dependent, averaging 10–12 mg/day of

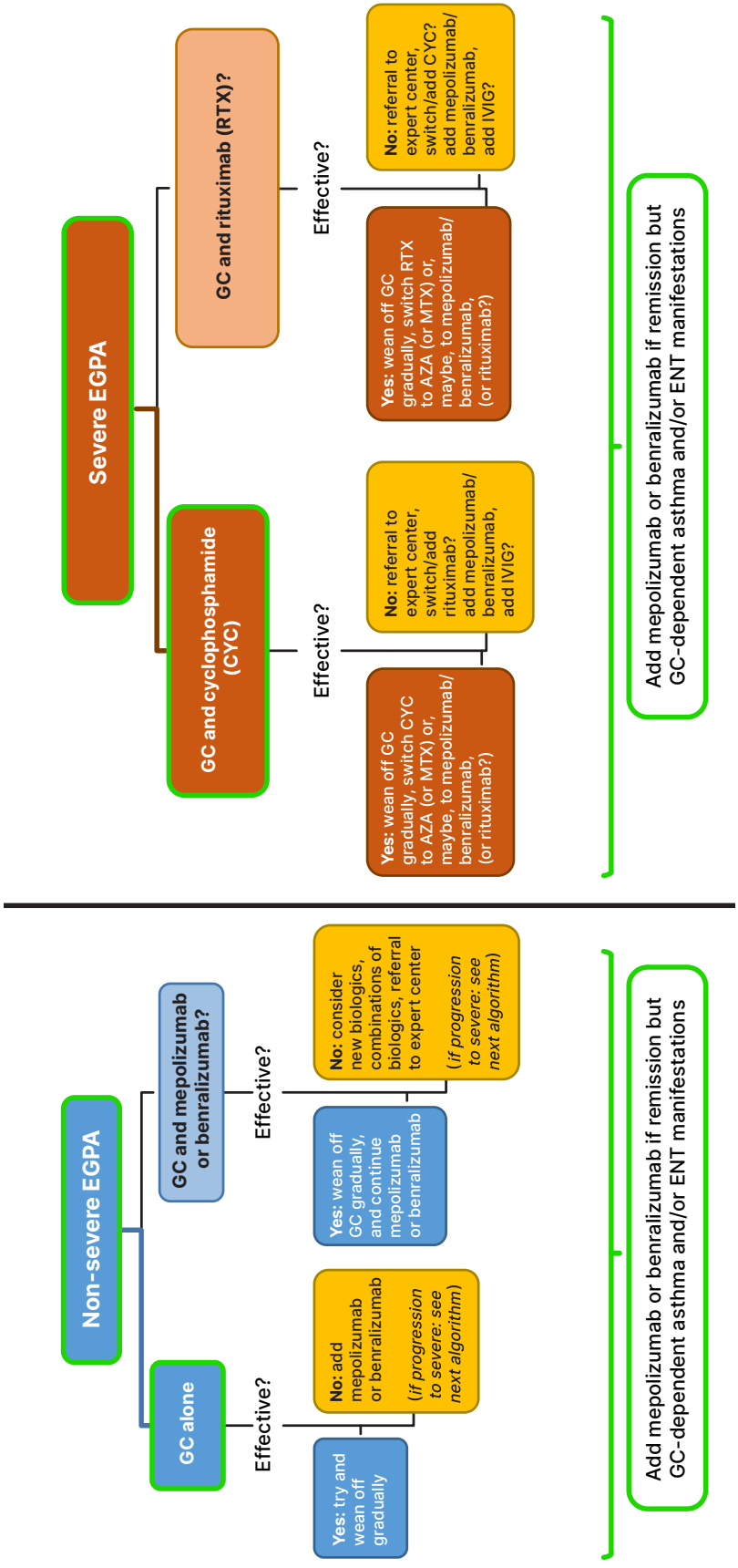

Figure 1. AZA: (oral) azathioprine (1.5-2 mg/kg/day); **CYC:** cyclophosphamide (oral 2 mg/kd/day, or IV pulses of 15 mg/kg at days 1, 15, 30 and then every 3 weeks for 3-9 months; dose adjusted to age and renal function); **ENT:** ear, nose, throat; GC: glucocorticoids (usually, and initially, prednisone 0.5-1 mg/kg/day, not exceeding 80 mg/day for 2 to 4 weeks, and then gradually tapered every 2 weeks; can be preceded by methylprednisolone IV pulses for severe forms 500-1000 mg/day for 1-3 days); *courtesy of Jason K. Lee, MD and Christian Pagnoux, MD.*

Abbreviations: IVIG: intravenous immunoglobulin; **MTX:** methotrexate (oral or subcutaneous, 20-25 mg/week); **RTX:** rituximab (1 g IV at day 1 and 15 for induction; 500 mg every 6 months if used for maintenance [scarce data to date on RTX for maintenance in EGPA]).

prednisone-equivalent, because of their asthma or ENT symptoms. Chronic GC use is associated with numerous complications, including osteoporosis, diabetes, coronary artery disease, and infections.[12] The advent of biologics has provided opportunities to minimize glucocorticoid exposure. Mepolizumab and benralizumab have been shown to substantially reduce prednisone requirements, with some patients achieving GC-free remission.[16] However, the MIRRA and MANDARA studies only enrolled patients at least 6 months after their EGPA diagnosis or after their last flare.[9] Earlier use of mepolizumab or benralizumab could likely decrease the rate of GC-dependency in EGPA or help earlier weaning off GC, but this requires further study. Personalized treatment plans should aim at balancing disease control and treatment toxicity.

Real-World Data and Long-Term Outcomes

While clinical trials provide critical insights, real-world data offers valuable perspectives on the effectiveness and safety of therapies. Registries and observational studies have thus far corroborated the efficacy of biologics in EGPA patient populations, including those with refractory disease.[16] Notably, the durability of remission and patient-reported outcomes, such as quality of life, have emerged as key metrics for evaluating therapeutic success.[7,17]

Whether these biologics should be administered for life or can be gradually discontinued after a few years needs to be studied. Trials in asthma have already begun to determine who can stop these treatments without experiencing an early relapse. The results from these studies and from other non-EGPA populations will likely guide future treatment approaches and/or studies for EGPA more specifically.

Future Directions

Emerging therapies targeting novel pathways, such as eosinophil trafficking and T-cell activation, hold promise for expanding treatment options. Anti-Siglec-8 monoclonal antibodies and Janus kinase (JAK) inhibitors are currently under investigation, with preliminary results indicating significant eosinophil suppression and potential efficacy in refractory EGPA.[18,19] Additionally, biomarker-driven approaches, including blood eosinophil counts, ANCA status, and possibly some genetic markers, may facilitate more precise patient stratification and therapy selection.

Conclusion

The therapeutic landscape for EGPA in 2025 reflects a paradigm shift toward personalized, pathogenesis-driven care. Biologics such as mepolizumab and benralizumab, now approved for EGPA, have transformed disease management by offering improved remission rates and reduced treatment toxicity. Ongoing research and real-world data will continue to refine these approaches, ensuring optimal outcomes for patients with this challenging disease.

Correspondence

Jason K. Lee, MD
Email: jason.k.lee.md@gmail.com

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About the Author

Ajit Johal, BSP, RPh, BCPP, CTH

Dr. Ajit Johal has been providing immunizations and clinical education since 2012. As a community pharmacist, he is an accessible provider of immunizations to patients in the community. In 2018, he started an organization called immunize.io with a mission statement of "taking our best shot at immunizing the world". Through "immunize.io," he has worked with numerous organizations and communities to address "vaccine hesitancy" and improve vaccine access locally, nationally, and globally. He champions community pharmacists as leaders of immunization services and presents on this topic at a national and global level. Ajit is also a clinical assistant professor for the University of British Columbia Faculty of Sciences program. At UBC, he has coordinated an elective course for UBC pharmacy students in travel health and immunizations.

Affiliations: Clinical Assistant Professor, University of British Columbia, Vancouver, B.C.

Recommended Vaccinations for Adults: What Respirologists Need to Know

Ajit Johal, BSP, RPh, BCPP, CTH

Patients with underlying respiratory comorbidities such as chronic obstructive pulmonary disease (COPD) are at greater risk of severe manifestations of the following vaccine-preventable diseases: COVID-19, influenza, herpes zoster, pertussis, pneumococcal disease, and respiratory syncytial virus (RSV). The following case illustrates how respirologists can recommend and support important patient vaccination updates.

Case:

A 76-year-old male patient who has been living with chronic obstructive pulmonary disease (COPD) for 5 years. His current medication regimen includes salbutamol (Ventolin MDI) 100 mcg, 1–2 puffs every 4 hours as needed, tiotropium (Spiriva Respimat) 2.5 mcg, 2 inhalations once daily, atorvastatin 40 mg once daily, and ramipril 10 mg once daily. The patient has received the seasonal influenza vaccination (HD-QIIV), and 3 doses of the COVID-19 primary series (last dose 18 months ago).

Chief Complaint

The patient's chief complaint is ongoing dyspnea and increased salbutamol use despite being adherent to long-acting muscarinic antagonist (LAMA) therapy. The patient has been under the care of a respirologist following the initial diagnosis of COPD 5 years ago.

Introduction

This patient is coming to their respirologist to optimize the management of their COPD, specifically on addressing airflow limitation, which presents as shortness of breath at rest. There is an opportunity to improve bronchodilation and review and update the patient's vaccination status.

Despite the approval and subsequent recommendation from the National Advisory Committee on Immunization (NACI) for vaccinations to protect against shingles, pneumococcal disease, and respiratory syncytial virus (RSV), adult immunization rates remain low. Furthermore, even programmatic vaccinations for seasonal influenza, pneumococcal disease and updated Coronavirus Disease 2019 (COVID-19) vaccinations remain below target levels for high-risk groups.[1]

Respirologists play an important role in improving recommended vaccination rates among high-risk patients with chronic lung conditions. Given their specialist role, a vaccination assessment and subsequent recommendation from a respirologist can have a positive impact to improve vaccination uptake in these patients. This article reviews the recommended vaccinations and how respirologists can support their patients in accessing them. **Table 1** provides a summary of the vaccinations recommended by NACI for patients with chronic lung conditions, including the funding and access pathways for administration.

COVID-19

The recent NACI statement on COVID-19 vaccination, applicable for all of 2025 and the summer of 2026, recommends a COVID-19 vaccine for previously vaccinated individuals who are at increased risk of Severe Acute Respiratory Syndrome Corona Virus 2 (SARS-COV-2) exposure or severe COVID-19 disease.[2] For patients with underlying lung conditions as defined in the "underlying medical conditions associated with more severe COVID-19 disease: a clinicians guide", including bronchiectasis, COPD, interstitial lung disease, pulmonary hypertension, and pulmonary embolism,[3] an up-to-date COVID-19 vaccine should be administered every Fall/Winter to reduce the risk of COVID-19 disease and its complications.

In this case, the patient is not up-to-date on their COVID-19 vaccinations according to their age (65+ years) and chronic conditions (COPD). Based on this, we recommend that the patient receive their updated COVID-19 KP.2 variant vaccine at the pharmacy during the 2024–2025 season.

Influenza

Seasonal influenza vaccination has been a longstanding recommendation for patients with chronic lung conditions. For patients aged 65+ years, NACI recommends a high-dose or adjuvanted vaccine to provide a better immune response.[4]

In this case, our patient has received their seasonal influenza vaccine, noting that they received the high-dose version since they are aged 65+ years.

Herpes Zoster (Shingles)

Since 2018, NACI has strongly recommended the recombinant zoster vaccine (Shingrix) for all patients aged 50+ years.[5] Herpes zoster, also known as shingles, is the reactivation of a primary chickenpox infection contracted earlier in life. It manifests as a painful blistering rash that does not cross the midline of the body. Complications can include post-herpetic neuralgia, which can occur in up to 1/5 of cases.[6] A meta-analysis of patients with chronic medical conditions shows that underlying medical conditions such as COPD and asthma increase the risk of latent reactivation of herpes zoster.[7]

In this case, our patient is aged 50+years and has the additional risk factor of COPD. Based on this, we recommend that the patient receive 2 doses of the recombinant zoster vaccine (spaced 2–6 months apart) at the pharmacy.

Pertussis

In Canada, it is recommended that adults receive a booster dose of the Tetanus/Diphtheria vaccine every 10 years as part of routine immunization programs. At least 1 of these booster doses should contain pertussis and be administered as a combination vaccine that

Vaccination	Dosing	Products	Funding	Access
COVID-19	Updated Vaccination in the Fall	Comirnaty® Spikevax	Publicly funded across all provinces	Community Pharmacy
Influenza	Updated Vaccination in the Fall	Fluad® (Adj-TIV) Fluzone® HD (HD-QIIV)	Publicly funded across all provinces	Community Pharmacy
TDAP	Every 10 years	Boostrix® Adacel®	Publicly funded in some provinces, some private pay	Community Pharmacy (British Columbia, Quebec) Doctor's Office Public Health Unit
Herpes zoster	2 doses (IM) at 0, 2–6 months *No booster recommended at this time	Shingrix®	Publicly funded in some provinces for select age groups, most are private pay	Community Pharmacy Doctor's Office
Pneumococcal	1 dose (IM) *No booster recommended at this time	Prevnar ®20 CapvaxieTM	Publicly funded in some provinces for select age groups, most are private pay	Community Pharmacy Doctor's Office
RSV	1 Dose (IM) *No booster recommended at this time	Arexvy® Abrysvo®	Publicly funded in some provinces for select age groups, most are private pay	Community Pharmacy Doctor's Office

Table 1. Vaccinations recommended by the National Advisory Committee on Immunization (NACI) for patients with chronic lung conditions; *courtesy of Ajit Johal, BSP, RPh, BCPP, CTH.*

Abbreviations: COVID-19: Coronavirus Disease 2019, **TDAP:** tetanus, diphtheria, pertussis, **IM:** intramuscular, **RSV** respiratory syncytial virus.

includes tetanus, diphtheria, and pertussis (TDAP). Pertussis, also known as "whooping cough," can be problematic in patients with underlying respiratory comorbidities.[8]

In this case, our patient has not received a tetanus/diphtheria vaccine since childhood. Based on this, we recommend a TDAP booster, which may be administered at the pharmacy, depending on the province.

Pneumococcal Disease

The bacterial pathogen Streptococcus pneumoniae (*S. pneumoniae*) is a common culprit of respiratory and invasive disease in adult patients. In a recently updated NACI statement on pneumococcal vaccination in adults, the multi-valent conjugate vaccines PCV20 (Prevnar 20) or PCV21 (Capvaxive) are strongly recommended for adults aged 65+ years and for those aged 18+ years with certain underlying conditions. For patients with chronic lung conditions, those with COPD, emphysema, bronchiectasis, interstitial lung disease, cystic fibrosis, and asthma that required medical care

in the preceding 12 months, are prioritized for vaccination.[9]

In this case, our patient is aged 65+ years and has an underlying chronic lung condition. The patient has also not received a pneumococcal vaccination in the past. Note that even if the patient had previously received a pneumococcal vaccination, NACI recommends PCV20/21 for updated protection if at least a year has passed since their last vaccination. We recommend that the patient receive a dose of PCV20 or PCV21 at the pharmacy.

Respiratory Syncytial Virus

RSV is a well-known illness in the pediatric population, but it can also lead to hospitalization for older adults, especially those with comorbidities. A review of RSV hospitalizations over 3 seasons in New York demonstrated that patients with underlying COPD were 4–13 times more likely to be hospitalized from an RSV infection compared to their age-matched peers.[10] The most recent statement from NACI on RSV strongly recommends adjuvanted (Arexvy) or bivalent (Abrysvo) RSV vaccines for older adults aged 75+ years, especially those with underlying medical risk factors.[11] Providers may also recommend vaccination to a broader population with the adjuvanted (Arexvy) RSV vaccination approved for adults 50+ and bivalent (Abrysvo) RSV vaccination indicated for adults 60+ as per the Health Canada product label and updated NACI statement on RSV vaccination in older adults.[12]

In this case, our patient is both aged 75+ years and has underlying COPD. We recommend that the patient receive an RSV vaccine at the pharmacy.

Supporting Vaccine Access in Specialist Care

In our case, the following vaccinations are recommended based on the patient's immunization history, age, and medical risk factors according to guidance from NACI.

- **Updated COVID-19 KP.2 vaccine**
- **Recombinant Zoster Vaccine – 1 dose now then the second dose in 2–6 months**
- **TDAP vaccine**
- **Pneumococcal Conjugate (PCV20/21) vaccine**
- **RSV (Adjuvated/Bivalent) vaccine**

While it is not expected that medical specialists such as respirologists maintain a vaccine refrigerator and administer vaccinations in their practice, a strong recommendation from a medical professional has been shown to increase vaccine uptake.[13]

Discussing recommended vaccinations and providing a prescription or consult note to the patient's primary care provider can support the pathway to administration. In some jurisdictions (British Columbia, Alberta, Quebec), pharmacists can independently administer vaccinations without a prescription.

Many medical professionals abstain from recommending vaccinations that are not covered by public programs. In these situations, patients must pay out of pocket for recommended vaccinations such as shingles, pneumococcal, and RSV. Ironically, despite most medical professionals considering cost as the greatest barrier for patients accepting a non-funded vaccine, the greatest barrier is, in fact, the absence of their recommendation.[14] Therefore, healthcare professionals who interact with patients diagnosed with chronic lung conditions should recommend all relevant vaccinations to provide an opportunity to mitigate risk.

As with any case report, the results should not be interpreted as a guarantee or warranty of similar results. Individual results may vary depending on the patient's circumstances and condition.

Correspondence

Ajit Johal, BSP, RPh, BCPP, CTH
Email: ajitjohal21@gmail.com

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About the Authors

Simon Couillard, MD, MSc

Dr. Simon Couillard is a Canadian specialist in respiratory medicine, researcher, and assistant-professor at the Université de Sherbooke (Sherbrooke, Canada). He finished a two-year clinical research fellowship in severe asthma and graduated with distinction from the University of Oxford MSc in experimental and translational therapeutics. His research themes are biomarker-guided prediction, prevention and management of airways disease. He leads an international collaboration with the Universities of Oxford-Leiden on biomarker-centred risk prediction in asthma (the ORACLE project).

Affiliations: Faculté de Médecine et des Sciences de la Santé, Université de Sherbrooke, Sherbrooke (Québec)

Philippe Lachapelle, MD

After completing his residency in pulmonology at McGill University, Dr. Lachapelle pursued a one-year subspecialty training at McGill University in sleep medicine and asthma. He then completed additional training at the Royal Melbourne Hospital (RMH) in Australia, where he undertook a two-year program in asthma and phenotyping. Dr. Lachapelle received comprehensive training in inflammometry of airway diseases and is equipped to integrate these techniques into both clinical practice and research. Since 2018, he has been working as a pulmonologist at the CIUSSS de l'Estrie and as an Assistant Professor at the University of Sherbrooke.

Affiliations: Faculté de Médecine et des Sciences de la Santé, Université de Sherbrooke, Sherbrooke (Québec)
Pneumologue, CIUSSS de l'Estrie - Centre Hospitalier Universitaire de Sherbrooke
Professeur adjoint / Assistant Professor, Université de Sherbrooke

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De-Escalation of Severe Asthma Therapy: Do We Wean the Biologic or the Inhaler First?

Simon Couillard, MD, MSc
Philippe Lachapelle, MD

Introduction

Asthma is a chronic respiratory disease affecting approximately 10% of Canadians.[1] The disease is recognized by the presence of classical symptoms (dyspnea, wheezing, chest tightness, cough, and sputum), combined with objectively measured variable airflow obstruction.[2] However, the simplicity of this definition overlooks one of the driving features of severe disease, type-2 inflammation, which is the single most treatable immune process.

Over the past two decades, research has redefined asthma as a heterogeneous disease,[3] recognizing type-2 inflammation as a prevalent, measurable, and treatable pathway.[3-5] In clinical settings, the type-2 inflammatory phenotype is identified by the presence of increased blood/sputum eosinophils and/or elevated levels of exhaled nitric oxide (FeNO).[6] With severe disease, this immune pathway remains active and is otherwise suppressed by corticosteroids in over 90% of patients.[7] Indeed, the cornerstone of asthma therapy–inhaled corticosteroid and biologics–primarily functions by suppressing type-2 inflammation, with a failure to suppress this pathway being associated with adverse outcomes and, most frequently, necessitates the use of biologics.[4,5,8-10]

The approval and use of six monoclonal antibodies to treat people with severe asthma have led to extraordinary benefits for patients. The currently approved biologics include omalizumab, which targets immunoglobulin (Ig) E; mepolizumab, reslizumab, and benralizumab, which target interleukin (IL)-5/5receptor(R), and finally, dupilumab and tezepelumab, which target IL-4R and thymic stromal lymophoietin (TSLP), respectively. Although omalizumab was primarily trialled in moderate allergic asthma, the latter five biologics (anti-IL-5/5R, anti-IL-4R, and anti-TSLP) have shown marked efficacy in severe asthma. These biologics have achieved a 50% reduction in annual severe asthma attack rates over placebo, a 50% reduction in the need for maintenance oral corticosteroids (OCS) in three of the biologics,[11] and significant improvements in lung function and symptom scores. The benefits are most pronounced in patients with high type-2 inflammation, with approximately 30% of these patients achieving near-normalization of asthma parameters, an endpoint referred to as 'remission'.[12]

Interestingly, the move toward remission has introduced a novel goal of therapy: avoiding high-dose inhaled corticosteroids (ICS).[13] Conversely, the astronomical cost of biologics has led clinicians to suspect that life-long therapy with these drugs may not be necessary for everyone, and may not be financially sustainable for societies. Thus, in this new era of asthma treatment, which allows for disease remission with biologics, the pressing question arises: should we wean off the biologic or the inhaler first?

Methodology

Given that maintenance OCS are now rarely used, and the benefit of some auxiliary maintenance therapies—such as montelukast, long-acting muscarinic antagonists, and macrolides—is limited in the context of type-2 inflammation, decisions to discontinue these treatments are generally made independently for patients eligible for biologics. Therefore, our discussion will focus on two main options for treatment de-escalation: should we prioritize weaning biologics or high-dose ICS? Our brief, narrative review of the evidence is limited to randomized controlled trials, as retrospective or observational studies on drug withdrawal are inherently affected by indication bias (i.e., only low-risk patients tend to be weaned).[14]

Weaning Biologics: Why, Which, How?

The Why

Although biologics are well tolerated,[10] their costs are high. A 2018 report by the Institute for Clinical and Economic Review[15] estimated the annual price for marketed biologics to be between $27,800–$31,000 USD. Discouragingly, at these prices, the incremental cost-effectiveness ratio per Quality-of-Life-Year in severe asthma reached $325,000–$391,000. It is important to emphasize that these estimates are based on US market prices, which may not reflect the actual price paid by payers. Nevertheless, these costings make a strong case for either discontinuing or extending the dosing interval of biologics in asthma treatment.

The Evidence

Anti-IgE: Omalizumab

As the oldest biologic approved for use in asthma treatment, omalizumab has the most data available regarding its discontinuation. In the XPORT trial,[16] 176 moderate-to-severe allergic asthmatics who had been on omalizumab for ~5 years were randomized 1:1 to either drug discontinuation or drug continuation. The cessation of omalizumab resulted in 40% more people experiencing exacerbations in the following year (67% versus 48%; absolute difference 19%; 95% confidence interval [CI] 533%). Whilst half of the people who discontinued the drug experienced no exacerbations, the difference and overall effect on asthma control symptoms supported the continued use of omalizumab.

We are not aware of randomized trials for extending dosing intervals of omalizumab.

Anti-IL-5/5R: Mepolizumab, Benralizumab, Reslizumab

The COMET trial[17] was a randomized placebo-controlled multicentre study of 295 patients who had been receiving mepolizumab for ≥3 years. Participants were randomized 1:1 to either discontinue mepolizumab (switch to placebo) or continue the treatment. The results are clear: within 4 weeks, blood eosinophil levels increased, and within 12 weeks, those who stopped mepolizumab experienced reexacerbation and/or loss of asthma control (hazard ratios [95% CI]: 1.61 [1.17-2.22] and 1.52 [1.132.02], respectively).

Recently, the publicly funded OPTIMAL trial[18] was conducted in Denmark. This open-label trial involved patients who had been on anti-IL-5/5R therapy for ≥1 year. A total of 73 participants were randomized 1:1 to progressively extend the drug interval versus maintain unchanged intervals. As a pilot study, it was found that extended intervals were associated with a higher number of exacerbations (37% versus 17%).

Together, these results suggest that discontinuing anti-IL-5 or extending the interval of anti-IL-5/5R therapy reverts the clinical condition to its pre-anti-IL-5/5R state.

Dupilumab

We are not aware of any randomized trials investigating the cessation or extended interval strategy for dupilumab.

Tezepelumab

The DESTINATION long-term extension study of tezepelumab trials included a 40-week double-blind comparison of cessation after 2 years of treatment with tezepelumab versus placebo.[19] As observed in the COMET trial for mepolizumab, tezepelumab discontinuation led to a gradual increase in blood eosinophils and FeNO starting at 4 weeks. A decline in asthma control, as indicated by symptom scores and lung function, was observed after 10 weeks. Encouragingly, for this upstream-acting biologic, suppression of IgE was maintained for up to 40 weeks, and 73% of patients who stopped tezepelumab remained exacerbation-free at 40 weeks. These results suggest that while upstream/alarmin-targeting biologics provide some sustained efficacy after withdrawal, their effectiveness remains temporary.

Bottom Line for Weaning Biologics

Despite a strong financial argument in favour of eventually weaning off biologics in severe asthma, no biologic has been shown to maintain asthma control and suppress type-2 inflammation (as measured by blood eosinophils and FeNO) after discontinuation. We note that these studies were conducted in adults. Investigating the potential for remission/cure of asthma in pediatric patients, who may start biologic treatment at age 6, as they transition to adulthood would be worthwhile.

Weaning ICS: Why and How?

The Why

Despite ICS being the cornerstone of asthma therapy, there is relatively little evidence to support the use of high-dose ICS in severe asthma. In fact, for most asthmatics, 90% of the therapeutic benefit of ICS is obtained at low doses (fluticasone propionate-equivalent <250 mcg/day).[20] However, the therapeutic advantages of higher dosing become more apparent in patients with pronounced and nonsuppressible type 2 inflammation.[21,22] Certainly, recent large cohort studies have reported that cardiovascular events, pulmonary embolism, type 2 diabetes, osteoporosis, and pneumonia are more likely to occur with high- versus low-dose ICS. This dose-dependent risk of corticosteroid toxicity raises questions about our acceptance of life-long high-dose ICS in severe asthma.[23,24] Finally, definitions of asthma 'remission' are moving toward requiring patients to be on at most medium-dose ICS.[13]

Tapering ICS as a therapeutic objective may be even more important for patients with mixed (eosinophilic and neutrophilic) inflammation, which is often found in patients with chronic airway remodelling.[25] While biologics directly suppress type-2 inflammation, it is now clear that asthma attacks are heterogeneous in nature.[4,26] In patients on anti-IL-5/5R therapies, these attacks are frequently associated with elevated neutrophilic cell counts and infections.[27-29] The infectious risks associated with OCS use are well established in both pulmonology and other medical specialties. OCS use has been linked to an increased risk of mycobacterial infections, fungus colonization, and bacterial superinfections.[30] With the growing interest in reducing ICS use among patients receiving biologics, emerging evidence now highlights infectious risks associated with high-dose ICS—such as increased risk of pneumonia and mycobacterial colonization—similar to what has been observed in chronic obstructive pulmonary disease.[23,24,31] Therefore, tapering ICS in patients on biologics may not only reduce side effects but also help prevent non-type-2 exacerbations by lowering the burden of bronchial infections.

The Evidence

To date, only one randomized trial has investigated ICS weaning under biologics. In the SHAMAL trial,[32] 208 patients who had been established and responding to benralizumab for ≥3 months were randomized 3:1 to either taper their high-dose ICS down to an as-needed dose or continue their highdose ICS-formoterol therapy over a 48-week period. Overall, 96% of patients were able to achieve and maintain some level of ICS reduction, with 61% relying soley on an anti-inflammatory reliever. Pointedly, there was a numerical increase in exacerbations for 'weaners' during the reduction period (0.15 versus 0.04 exacerbations per person-year, rate ratio [95% CI] 3.67 [0.49-27.55). Moreover, the 'weaners' experienced a loss of 89 mL in forced expiratory volume in the first second (FEV1) during the study, with greater reductions observed in those reaching an as-needed ICS dose, which was associated with increases in FeNO. Reducing to low-to-medium-dose ICS seemed to alleviate the risk of lung function deterioration. Hence, while ICS weaning under anti-IL-5R therapy may be possible, it is advisable to decrease to no more than medium-dose ICS, or closely monitor FeNO levels.

We are aware of conference abstracts that analyze phase 2 trial results for the withdrawal of ICS under dupilumab.[33] While the results are promising, they have not yet been peer-reviewed or published beyond the initial phase 2 trial report.[34] Additionally, a trial for ICS withdrawal under tezepelumab is currently recruiting (NCT06473779).

To Wean or Not to Wean?

Summarizing the data in **Table 1**, we can draw several conclusions.

First, although it may be enticing to avoid the high costs of biologics, trials that have investigated discontinuing or spacing out drug intervals for biologics in severe asthma have led to an increase in adverse outcomes for patients weaning off them. In view of the strong therapeutic efficacy and relative innocuity of biologics compared to asthma attacks and OCS, one may argue that, if biologics were cost-free, the idea of weaning off of them would never even be considered. Conversely, high-dose ICS may be toxic and their therapeutic efficacy is unclear compared to low-dose ICS. However, we concede that these inhalers are remarkably inexpensive and accessible (**Figure 1**).

Biologic (*Mechanism*)	Stopping Biologic	Extending Biologic Intervals	Weaning ICS
Omalizumab (anti-IgE)	**XPORT**[16] Worst outcomes		
Mepolizumab (anti-IL-5)	**COMET**[17] Worst outcomes	**OPTIMAL**[18] Worst outcomes	
Reslizumab (anti-IL-5)			
Benralizumab (anti-IL-5R)			**SHAMAL**[32] Reduction to medium-dose ICS or for patients with low FeNO levels appears safe
Dupilumab (anti-IL-4R)			**Phase 2 trial post hoc analysis** ? (communicated, manuscript under review)
Tezepelumab (anti-TSLP)	**DESTINATION**[19] Worst outcomes		**ARRIVAL** ? (Recruiting: NCT06473779)

Table 1. Summary of Trials on the Weaning of Biologics or ICS in Severe Asthma; *courtesy of Simon Couillard, MD, MSc and Philippe Lachapelle, MD.*

Grey shaded boxes indicate the absence of trial data. There might be retrospective or observational data, but we did not consider these study designs as adequate to answer the research question.

Abbreviations: FeNo: fractional exhaled nitric oxide, **ICS:** inhaled corticosteroid, **IgE:** immunoglobulin E, **IL:** interleukin, **TSLP:** thymic stromal lymphopoietin.

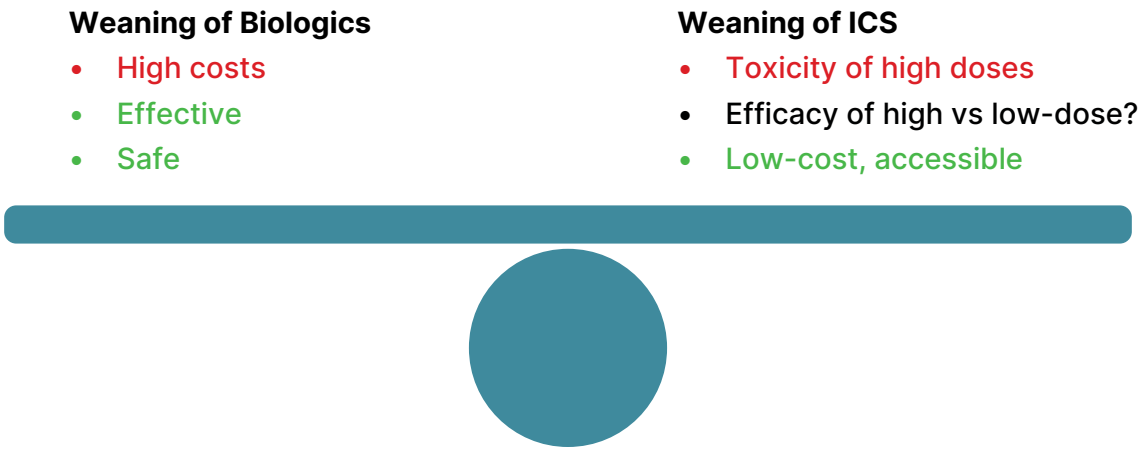

Figure 1. The Balance of Features to Push for the Weaning of Biologics *versus* Inhaled Corticosteroids (ICS); *courtesy of Simon Couillard, MD, MSc and Philippe Lachapelle, MD.*

Second, high-dose ICS may cause substantial harm and offers limited therapeutic benefits for most severe asthmatics. Achieving remission has become an attractive outcome encouraging the reduction to at most medium-dose ICS. This second objective is further supported by the innovative SHAMAL study and other promising ongoing research. These developments lead us to hope that by 2028, we will be striving to avoid high-dose ICS in patients established on biologics.

Conclusion

To conclude, selecting the appropriate biologic and ICS for each patient will always remain the first and foremost question in our minds. By continually questioning our therapeutic decisions, studying them, and re-assessing the need for each therapy for modern-day asthmatics, we can achieve the best possible outcomes for our patients. Rheumatoid arthritis and inflammatory bowel disease patients are maintained in remission without additional maintenance therapy, so why not aim for the same for those with asthma?

Correspondence

Simon Couillard, MD, MSc
E-mail: s.couillard@usherbrooke.ca

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