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

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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 lymphopoietin (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 Review¹⁵ 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 trial¹⁷ 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 [1.13–2.02], respectively).

Recently, the publicly funded OPTIMAL trial¹⁸ 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 high-dose 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 solely 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.

Weaning of Biologics

- High costs
- Effective
- Safe

Weaning of ICS

- Toxicity of high doses
- Efficacy of high vs low-dose?
- Low-cost, accessible



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?

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