Therapeutics Initiative
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THERAPEUTICS LETTER 145
October 2023

Minimizing inhaled corticosteroids for COPD

Chronic Obstructive Pulmonary Disease (COPD) is characterized by airway inflammation and irreversible airflow obstruction that cause shortness of breath, cough, and excess mucus production, reducing quality of life. Permanent anatomical changes make bronchodilators less effective for COPD than for asthma.

Cigarette smoking is the principal cause, although long-term exposure to other lung irritants (including air pollution) also contributes. Stopping smoking improves symptoms, and is the only effective strategy to slow disease progression and reduce premature mortality.[1]

Acute exacerbations of COPD and bronchitis, typically due to infection, ranked second only to childbirth as a cause of hospitalization in Canada in 2018–2019, exceeding heart failure and myocardial infarction.[2] By 2020–2021, they ranked eighth (after COVID-19), but still over 47,000 admissions/year. In British Columbia their ranking declines, overshadowed by substance use disorders and major mental illness.[3]

Clinical goals of drug therapy are to reduce symptoms, improve functional capacity, and prevent exacerbations. Drug therapy has not been shown to reduce mortality.[4]

Inhaled corticosteroids: the evidence

Recognizing their efficacy for asthma, doctors began to prescribe inhaled corticosteroids (ICS) for COPD in the 1980's, without evidence from randomized controlled trials (RCTs).[5] Two decades later, RCTs had shown no mortality benefit from ICS compared with placebo, no reduction in the proportion of people experiencing an exacerbation, and no improvement in quality of life.[6-8] A possible explanation is that while corticosteroids potently suppress eosinophilic airway inflammation in asthma, the neutrophilic inflammatory process in COPD is typically steroid resistant.[5]

Provincial, national and international guidelines all recommend limiting prescription of ICS to the most severe stages of COPD.[9-11] During 2017–21, 51,128 British Columbians initiated drug therapy for COPD, of whom 27% received an ICS alone or in combination. This proportion was stable over the 5 years.[12] It is lower than in a large United Kingdom sample, in which 47% of COPD patients still received ICS as a component of initial daily drug therapy during 2015 (down from 77% in 2005).[13]

Serious harms from chronic inhaled corticosteroid use include pneumonia and fractures,[14] updated here from an unpublished 2020 TI meta-analysis.[15]

COPD guidelines discourage routine ICS prescription

Rational drug therapy employs the simplest and least expensive treatment to achieve individual therapeutic goals. For **initial therapy**, BC (2020) and Global initiative for chronic Obstructive Lung Disease (GOLD, 2022) guidelines recommend short-acting beta agonists (SABA) or short-acting muscarinic antagonists (SAMA) to relieve shortness of breath.[9,11]

For **worsening symptoms or to reduce exacerbations**, both recommend short and then long-acting bronchodilators (beta agonists/LABA or muscarinic antagonists/LAMA), alone or in combination.

Outcome (harm)	RCTs reporting outcome	Findings of TI meta-analysis (NNH: weighted mean duration of ICS)
Pneumonia requiring hospitalization	49 RCTs (n = 57,027) Fluticasone: 32 RCTs (n = 46,877) Budesonide: 17 RCTs (n = 10,150)	Fluticasone vs. non-ICS: • RR 1.50 (95% CI 1.34 to 1.68)* • ARI 1.1%; NNH 93 (21 months) Budesonide vs. placebo: • RR 1.60 (95% CI 1.01 to 2.55)* • ARI 0.5%; NNH 188 (9 months)
Total fractures	20 RCTs (n = 25,936) Fluticasone: 18 RCTs (n = 23,079) Budesonide: 2 RCTs (n = 2,857)	Fluticasone/budesonide vs. non-ICS: • RR 1.28 (95% CI 1.07 to 1.54) • ARI 0.42%; NNH 240 (16 months)

RR: relative risk; ARI: absolute risk increase; NNH: number needed to harm; * independent of ICS dose, duration, or baseline severity of COPD

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ISSN 2369-8691

To LAMA + LABA, add ICS at the lowest possible dose **only for people who continue to experience repeated exacerbations**. GOLD and a 2020 Cochrane systematic review point out that no "escalation" strategy has been tested in RCTs,[11,16] while deprescribing ICS has been tested.

Can ICS be deprescribed safely?

Two recent manufacturer-funded studies evaluated ICS withdrawal, focusing on acute exacerbations, the most relevant clinical issue. Amongst 2,488 people with severe - very severe COPD who were susceptible to exacerbations, WISDOM (2014) **compared triple therapy** for up to 1 year (tiotropium 18 mcg/d + salmeterol 50 mcg twice/d + fluticasone 500 mcg twice/d) **with gradual withdrawal of fluticasone** over a 12-week period (followed by LAMA/LABA alone).[17] **Moderate or severe exacerbations were similar among people who discontinued or continued ICS therapy** (hazard ratio, 1.06; 95% CI 0.94 to 1.19). There were no clinically important between-group differences in symptoms, quality of life or safety. No patient subgroup had increased likelihood of exacerbations after stopping ICS.

Amongst 1,053 people **without frequent exacerbations**, SUNSET (2018) compared **continued triple therapy** for up to 26 weeks (tiotropium 18 mcg/d + salmeterol 50 mcg / fluticasone 500 mcg twice/d) **with abrupt discontinuation of ICS after long-term triple therapy**, replaced by once daily LAMA/LABA (indacaterol 110 mcg / glycopyrronium 50 mcg).[18] Annualized **moderate or severe exacerbations did not differ** between treatments (rate ratio 1.08; 95% CI 0.83 to 1.40). There was no difference in the time to first moderate or severe COPD exacerbation (hazard ratio 1.11; 95% CI 0.85 to 1.46).

SUNSET is the only RCT to report a pre-specified analysis of patient subgroups defined by baseline blood eosinophil counts, one approach to differentiating COPD (<300 cells/µL) from asthma (≥300 cells/µL). When baseline eosinophil count was <300/µL (COPD), stopping ICS made no difference to the rate of moderate or severe exacerbations, nor the time to exacerbation. In contrast, **in people with baseline eosinophils ≥300/µL (asthma/COPD overlap)**, stepdown to LAMA/LABA alone increased moderate or severe exacerbations vs. continuing ICS over 6 months (rate ratio 1.86; 95% CI 1.06 to 3.29).

Conclusions

- **Short-acting bronchodilators (SABA or SAMA), but not ICS, remain initial drug therapy for COPD.**
- **For persistent symptoms or exacerbations, adding LAMA or LABA, then LAMA + LABA, is recommended (but this strategy has not been tested in RCTs).**
- **For most people with COPD, the increased risk of serious harms from ICS outweighs the limited known benefits for symptoms or exacerbations.**
- **It is reasonable to try stopping ICS in clinically stable patients with infrequent exacerbations. For patients with eosinophils above 300/µL in a complete blood count, first taper ICS over a few months.**

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Multiple experts and primary care clinicians reviewed the draft of this Therapeutics Letter for factual accuracy, and to ensure it is relevant to clinicians.

The UBC TI is funded by the BC Ministry of Health to provide evidence-based information about drug therapy. We neither formulate nor adjudicate provincial drug policies.