

The dose of inhaled corticosteroids in patients with COPD: when less is better

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Background: The use of inhaled corticosteroids (ICS) in combination with bronchodilators in patients with COPD has been shown to decrease the rate of disease exacerbations and to improve the lung function and patients' quality of life. However, their use has also been associated with an increased risk of pneumonia.

Materials and methods: We have reviewed existing clinical evidence on the risks and benefits of ICS in COPD, including large randomized clinical trials, meta-analyses, and clinical reviews.

Results: A large body of evidence supports the clinical benefits of ICS in patients with COPD in terms of exacerbations, symptoms, lung function, and quality of life. The incidence of adverse events related to ICS, including pneumonia, varies strongly among the studies and seems to be dose dependent, with recent well-designed, large studies on low-dose ICS reporting similar safety profiles in ICS and non-ICS groups.

Conclusion: The benefits of ICS in COPD continue to outweigh the risks, especially when lower ICS doses are employed. Given that the data on ICS withdrawal in COPD are scarce and conflicting, we argue that using reduced doses of ICS could be an optimal strategy to manage patients with COPD.

Keywords: acute exacerbations, anti-inflammatory effects, COPD, asthma-COPD overlap syndrome, inhaled corticosteroids, lower doses of ICS, pneumonia

Introduction

A high and growing prevalence of COPD has been reported both globally and regionally. According to the estimations of Burden of Obstructive Lung Disease program and other epidemiological studies, the number of patients with COPD in 2010 was around 384 million worldwide.¹ Globally, there are around 3 million COPD-related deaths annually, with an increase in the prevalence of smoking, and of indoor air pollution from biomass cooking and heating in developing countries. This fact, and increased aged population in developed countries, led the WHO to estimate that the prevalence of COPD would increase over the next years, so that by 2030, there may be about 4.5 million deaths per year from this disease.² Despite recent trends in reduction of COPD standardized mortality rates and some success in anti-smoking efforts in developed countries, the overarching demographic impact of aging in an ever-expanding world population, combined with other factors such as high rates of smoking and air pollution ensure that COPD will continue to represent an ever-increasing problem in the 21st century.³

These overwhelming epidemiological data of COPD pose a huge challenge for clinicians, health care systems, and societies. Much of the burden of COPD is due to exacerbations, which are associated with increased disease progression,

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reduced quality of life, and increased costs, especially those related to hospitalization.^{4,5} The most recent strategy document from the GOLD advocates for a reduction of the risk of exacerbations as the central part of the pharmacological therapy for any patient with COPD.⁶ Goals of effective COPD management, including symptom relief, prevention of exacerbations and disease progression, improvement of health status, reduction of mortality, improved exercise tolerance, and prevention and treatment of complications should be reached at the cost of minimal side effects from treatment.⁷⁻⁹

However, despite the existence of effective pharmacological treatments, management in daily practice can be complex for different reasons. COPD is a heterogeneous chronic entity, patients often suffer from comorbidities, and long-term treatment is frequently required, which may increase the risk of adverse events and raise concerns about adherence to prescribed medications.¹⁰ At the same time, some subgroups of patients with COPD, such as those with greater lung function impairment, are highly susceptible to recurrent exacerbations that increase the severity of their condition.¹¹⁻¹⁴

Treatment of patients with COPD in daily practice continues to pose challenges for physicians to achieve the maximum benefit of non-pharmacological measures (eg, smoking cessation and rehabilitation) and pharmacological treatments (eg, bronchodilators and inhaled corticosteroids [ICS]) in the individual patient. All these options are relevant and effective. However, the usefulness of ICS in COPD has been questioned lately because of concerns about potential side effects such as pneumonia. Importantly, high doses of ICS are commonly prescribed to COPD patients, with trials involving doses of 1,000 µg fluticasone propionate per day during 2–3 years,^{15,16} whereas it is becoming increasingly clear that most ICS adverse reactions are dose related, and using lower doses of ICS substantially reduces the risk of undesired effects.¹⁷ Therefore, it is a convenient time for revising the role of ICS in the management of COPD based on the recent clinical data of efficacy, safety, underlying physiopathology mechanisms, and dose-response effects, all of which affect the benefit–risk balance of ICS. To this purpose, a comprehensive review of MEDLINE/PubMed and the Cochrane Library databases was made. Search MeSH terms included “chronic obstructive pulmonary disease”, “bronchodilator agents”, “administration/inhalation”, “glucocorticoids”, “beta-adrenergic antagonists”, “muscarinic antagonists”, “pneumonia”, and “quality of life”. References of retrieved articles were cross-checked for additional studies.

Efficacy of ICS in the management of patients with COPD

A number of randomized controlled clinical trials have provided evidence of the higher efficacy of ICS combined with a long-acting beta₂-adrenoreceptor agonist (LABA) compared to placebo in reducing exacerbations (between 24% and 41%) and improving the lung function (mean change in FEV₁ between 92 and 144 mL) and quality of life (mean difference in scores of the St George’s Respiratory Questionnaire [SGRQ] between 2.4 and 7.5).¹⁸⁻²⁰

Combinations of ICS/LABA also significantly reduced the yearly rate of moderate and severe exacerbations (between 25% and 30%) and improved the lung function and quality of life as measured by SGRQ score, when compared with LABA alone,^{19,21-25} particularly in patients with frequent exacerbations.²⁶⁻²⁸ The beneficial effects of combining ICS with LABA have also been confirmed in systematic reviews and meta-analyses.^{29,30} Although in the Towards a Revolution in COPD Health study, the difference between an ICS/LABA combination and LABA alone in all-cause mortality was not statistically significant ($P=0.052$),¹⁵ several observational studies showed that the use of ICS/LABA combination was associated with a reduced total mortality, compared with LABA monotherapy.^{22,31}

The beneficial effect of ICS in COPD patients is stronger for those with a concurrent asthma diagnosis or with a history of exacerbations. It has been estimated that the prevalence of asthma-COPD overlap syndrome among COPD patients is around 20%, and that these patients have a better prognosis when treated with ICS/LABA.^{32,33}

Safety of ICS in the management of patients with COPD Pneumonia

The impact of ICS use on the development of pneumonia has been heavily debated. An increased incidence of pneumonia associated with ICS was observed in several clinical trials including Towards a Revolution in COPD Health²⁵ and the Investigating New Standards for Prophylaxis in Reducing Exacerbations studies.¹⁶ It should be noted, however, that the protocols of these trials lacked the prospective definition of pneumonia (eg, confirmation by chest radiography), which might potentially lead to overdiagnosis of pneumonia. Other studies demonstrated no increased risk for pneumonia and no effects of ICS on pneumonia-related mortality.^{20,34,35} Systematic reviews and meta-analyses also provided conflicting results.^{36,37} Interestingly, the incidence of pneumonia reported in the most recent clinical trials on patients with COPD has decreased, which could be related to the usage of lower doses of ICS in

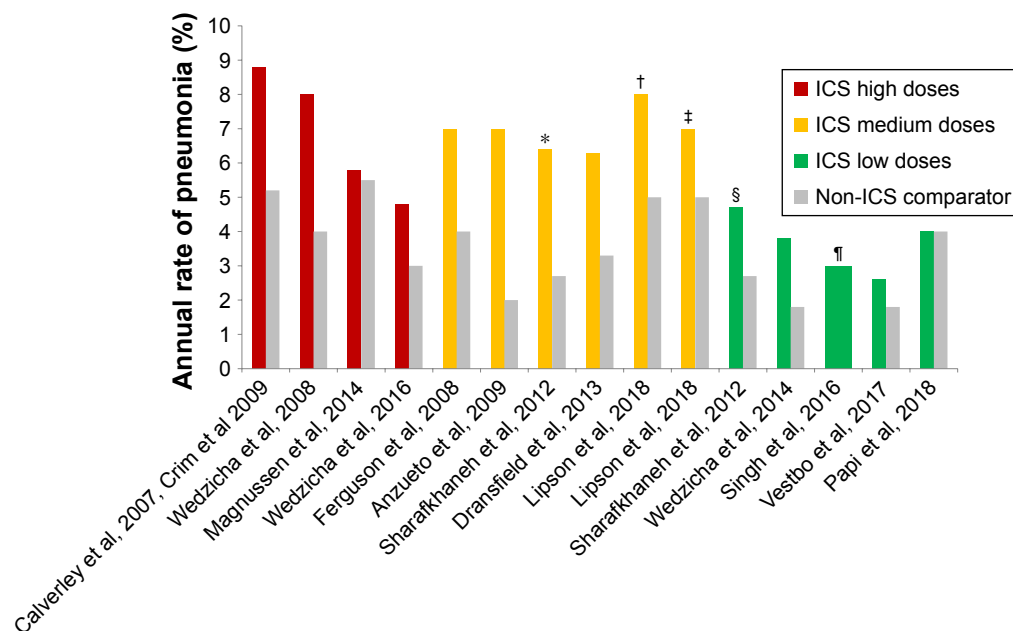


Figure 1 Incidence rates of pneumonia in different studies according to doses of ICS.

Notes: *Comparison between beclomethasone/formoterol 640/18 µg formoterol 18 µg. †Comparison between fluticasone furoate/umeclidinium/vilanterol vs umeclidinium/vilanterol. ‡Comparison between FF/vilanterol vs umeclidinium/vilanterol. §Comparison between beclomethasone/formoterol 320/18 µg formoterol 18 µg. ¶Both arms of the study were treated with ICS (extrafine BDP/FF/G 400/24/50 vs extrafine BDP/FF 400/24). Only ICS doses approved in COPD are considered.

Abbreviations: BDP, beclomethasone dipropionate; FF, fluticasone furoate; G, glycopyrronium; ICS, inhaled corticosteroids.

the treatment regimens (Figure 1). Thus, data from the recent TRINITY study, in which low doses of ICS were used in a fixed combination with a long-acting muscarinic antagonist and a LABA, showed that the incidence of pneumonia and of other adverse events was similar between the triple regimen and long-acting muscarinic antagonist monotherapy.³⁸

Concordantly, there is a consistent evidence of a dose-response effect for the link between ICS and pneumonia coming from observational studies. In a population-based cohort study of 163,514 patients with COPD treated with inhaled medications between 1990 and 2005 in the province of Québec, Canada, there were 20,344 patients who were identified as having had at least one episode of pneumonia.³⁹ After adjusting for differences in covariates in cases and controls, current use of ICS was associated with an increase in the rate ratio (RR) of pneumonia of 1.69, which was dose dependent, ranging from an RR of 1.24 for the lower doses to an RR of 1.86 with the highest doses of ICS (equivalent to fluticasone propionate 1,000 µg/day or more). Also, in a nested case-control study, the risk of hospitalization for pneumonia increased with ICS dose: while the RR for current use of ICS (all doses) was 1.70, the RR for the highest dose of ICS (equivalent to fluticasone propionate 1,000 µg/day or more) was as high as 2.25.⁴⁰ A higher ICS dosage has been found to correlate significantly with a higher load of typical airway bacteria in COPD patients⁴¹ and with an increased risk of *Mycobacterium tuberculosis* infection.⁴² In a recent

retrospective analysis of 23,013 patients with obstructive lung disease in the UK, patients receiving daily ICS doses in excess of 700 µg (fluticasone propionate equivalent) were significantly more likely (OR 2.38, 95% CI: 1.17–4.83; $P=0.001$) to have pneumonia compared with patients who were prescribed lower doses. Furthermore, irrespective of the dose, patients with extrafine particles of ICS (particles with a mass median aerodynamic diameter of 1.1 µm) were at a lower risk of pneumonia (adjusted OR 0.60, 95% CI: 0.37–0.97; $P=0.011$) and acute exacerbations (adjusted RR 0.91, 95% CI: 0.85–0.97; $P=0.001$) compared with those with ICS of larger particle size distribution profiles.⁴³

Systemic adverse effects

Prolonged use of ICS can cause systemic adverse effects. Systemic adverse effects related to the use of ICS in COPD have been addressed in a comprehensive systematic review and meta-analysis.⁴⁴ For most studied systemic adverse events, such as adrenal axis suppression, osteoporosis, and diabetes, a dose-dependent relationship was observed and is suggested to be limited by the partial systemic ICS absorption at high doses.^{42,44–48}

Benefit–risk balance of ICS

When assessing the benefit–risk balance of a treatment, it is important to take into account both the seriousness of the alleviated conditions and of the side effects and their

incidence. In COPD, moderate-to-severe exacerbations have been linked to disease progression, increased risk of further exacerbations, faster decline of pulmonary function, and higher risk of mortality.^{49–51} Interestingly, there has been no increase of pneumonia-related mortality in patients treated with ICS in clinical trials.⁵² As for the incidence, COPD exacerbations are much more frequent events than pneumonia, with >40% of patients reported to suffer moderate-to-severe exacerbations of COPD in clinical trials and the annual rates frequently surpassing one such exacerbation per patient per year, whereas only 2%–7% of patients experience pneumonia (Table 1).

Regarding the benefit–risk of the ICS dosage, two recently published studies have provided important information. In a randomized trial (IMPACT study)⁵³ involving 10,355 patients with COPD, 52 weeks of a once-daily fixed-dose combination of fluticasone furoate 100 µg, umeclidinium 62.5 µg, and vilanterol of 25 µg was compared with fluticasone furoate–vilanterol 100/25 µg and umeclidinium–vilanterol 100/62.5 µg. The dose of fluticasone furoate in the triple therapy could be comparable to 500 µg of fluticasone propionate and, therefore, considered a medium ICS dose. After 52 weeks of treatment, it was found that fluticasone furoate/umeclidinium/vilanterol significantly reduced the rate of moderate-to-severe exacerbations compared with furoate/vilanterol and umeclidinium/vilanterol, with a small increase in the incidence of total pneumonias in the arms with ICS vs the arms without ICS, 8% and 7% for the triple therapy and fluticasone furoate/vilanterol, respectively, vs 5% for umeclidinium/vilanterol.

The other recent randomized study in COPD was the TRIBUTE study,⁵⁴ in which an extrafine triple fixed combination of beclometasone, formoterol, and glycopyrronium (87/5/9 µg) twice daily was compared with a dual bronchodilator therapy of indacaterol plus glycopyrronium (85/43) in 1,532 patients with COPD. The dose of beclometasone in the extrafine triple therapy is considered a low ICS dose. After 52 weeks of treatment, it was found that extrafine beclometasone/formoterol/glycopyrronium significantly reduced the rate of moderate-to-severe exacerbations compared with indacaterol/glycopyrronium, without increasing the risk of pneumonia (incidence of pneumonia 4% in the two study groups).

Also, a recent assessment report of the European Medicines Agency of the risk of pneumonia in COPD patients treated with ICS concluded that the benefit–risk balance of ICS-containing products remained favorable, despite the increased risk of pneumonia associated with the ICS.⁴⁵

The report also emphasized that pneumonia was an intrinsic comorbidity to COPD in the presence of certain predisposing factors, and stressed the difficulties of the differential diagnosis of pneumonia and COPD exacerbations. The assessment concluded that the concept of a dose–response for the pneumonia risk had biological plausibility and should be counted as supportive clinical evidence.

Pathophysiological mechanisms of the benefit–risk balance of ICS

The dose–response curve for clinical response to ICS is relatively flat, in contrast to the steeper dose–response curve for ICS-related adverse effects (Figure 2).^{55,56} This implies that increasing the dose of ICS on the flat part of the efficacy curve may confer little additional benefit, but at the same time may considerably increase the chance of adverse effects, resulting in a worse clinical index.^{56–58} Of note, fluticasone propionate has the highest level of lipophilicity among ICS and prolonged systemic tissue retention, which, combined with high potency and affinity toward the glucocorticoid receptor, may explain in part its greater systemic activity compared with other available ICS. Indeed, high doses of inhaled fluticasone propionate have been associated with the greatest dose-related systemic bioactivity.⁵⁵

Optimizing the ICS dosage and minimizing the risk of adverse effects are especially relevant for patients with COPD, since they tend to be older and to have several comorbid conditions for which they are frequently multidrug users. All of these make them particularly susceptible to potential adverse effects of high-dose ICS treatment.⁵⁹

A favorable risk–benefit ratio of using lower doses of ICS while maintaining clinical efficacy is also supported by a growing trend differentiating between the predominantly immunosuppressive effects of high doses of ICS vs the predominantly anti-inflammatory effects of lower doses.^{45,60–62} It has been shown that ICS have the potential to modify cellular and humoral pathways of the immune networks of the lung that are required in normal conditions for efficient clearance of pathogens such as pneumococci.⁶⁰ The potential of high doses of ICS to inhibit the cellular components of the immune response involving alveolar macrophages, T-cells, and other signaling cytokines has been postulated based on the observed increased airway bacterial load and increased risk of mycobacterial infections, including cases of reactivation of pulmonary tuberculosis.^{39,41,42,59,60,63} By contrast, lower doses of ICS seem to exhibit predominantly anti-inflammatory effects with modulation of the humoral components of the innate immune response, which may lead to

Table 1 Characteristics and results of major long-term Phase III double-blind, randomized controlled clinical trials with ICS in patients with COPD

Study, year, reference	No of patients	Length of treatment	Tested products daily dose, µg	ICS daily dose, µg	ICS dose category ^a	Annual rate of moderate-severe COPD exacerbations		Incidence or annual rate of pneumonias	
						ICS	Control	ICS	Control
Calverley et al, 2007 ¹⁵ Crim et al, 2009 ¹⁶	6,184	3 years	FP/S 1,000/100 vs FP 1,000 vs S 100 vs placebo	FP 1,000	High	FP/S: 0.85; FP: 0.93	S: 0.97; placebo: 1.13	FP/S: 0.088; FP: 0.084 (annual rate)	S: 0.052; placebo: 0.052 (annual rate)
Wedzicha et al, 2008 ¹⁶	1,323	2 years	FP/S 1,000/100 vs T 18	FP 1,000	High	FP/S: 1.28	T: 1.32	FP/S: 8%	T: 4%
Magnussen et al, 2014 ⁴⁴	2,485	52 weeks	FP/T/S 1,000/18/50 vs T/S 18/50 (FP tapered off over 12 weeks)	FP 1,000	High	FP/T/S: 0.91	T/S: 0.95	FP/T/S: 5.8%	T/S: 5.5%
Wedzicha et al, 2016 ⁷⁵	3,362	52 weeks	FP/S 1,000/100 vs I/G 110/50	FP 1,000	High	FP/S: 1.19	I/G: 0.98	FP/S: 4.8%	I/G: 3.2%
Ferguson et al, 2008 ²⁴	782	52 weeks	FP/S 500/100 vs S 100	FP 500	Moderate	FP/S: 1.06	S: 1.53	FP/S: 7%	S: 4%
Anzueto et al, 2009 ²⁵	797	52 weeks	FP/S 500/100 vs S 100	FP 500	Moderate	FP/S: 1.10	S: 1.59	FP/S: 7%	S: 2%
Sharafkhaneh et al, 2012 ⁷⁷	1,219	52 weeks	B/FoF 640/18 vs B/FoF 320/18 vs FoF 18 ^b	B 640 or 320 ^b	Moderate, low	B/FoF 640/18: 0.70; B/FoF 320/18: 0.79	FoF: 1.07	B/FoF 640/18: 6.4%; B/FoF 320/18: 4.7%	FoF: 2.7%
Dransfield et al, 2013 ²⁶	3,255	52 weeks	FF/V 100/25 vs V 25	FF 100	Moderate	FF/V 100/25: 0.81	V: 1.11	FF/V: 6.3%	V: 3.3%
Lipson et al, 2018 ³³	10,355	52 weeks	FF/V/U 100/25/62.5 vs FF/V 100/25 vs V/U 25/62.5	FF 100	Moderate	FF/V/U 100/25/62: 0.91; FF/V 100/25: 1.07	V/U 25/62.5: 1.21	FF/V/U: 8%; FF/V: 7%	V/U: 5%
Wedzicha et al, 2014 ²⁸	1,186	48 weeks	Extrafine BDP/FoF 400/24 vs FoF 24	BDP 400	Low	BDP/FoF: 0.80	FoF: 1.12	BDP/FoF: 3.8%	FoF: 1.8%
Singh et al, 2016 ⁷⁸	1,368	52 weeks	Extrafine BDP/FoF/G 400/24/50 vs extrafine BDP/FoF 400/24	BDP 400	Low	BDP/FoF/G: 0.45; BDP/FoF: 0.56	NA	BDP/FoF/G: 3%; BDP/FoF: 3%	NA
Vestbo et al, 2017 ⁷⁸	2,691	52 weeks	Extrafine BDP/FoF/G 400/24/50 vs T 18+ extrafine BDP/FoF 400/24 vs T 18	BDP 400	Low	BDP/FoF/G: 0.46; T+BDP/FoF: 0.45	T: 0.57	BDP/FoF/G: 3%; T+BDP/FoF: 2%	T: 2%
Papi et al, 2018 ⁵⁴	1,532	52 weeks	Extrafine BDP/FoF/G 400/24/50 vs I/G 85/43	BDP 400	Low	BDP/FoF/G: 0.50	I/G: 0.59	BDP/FoF/G: 4%	I/G: 4%

Notes: ^aClassified according to Bassam M, Mayank V. Steroids in asthma: friend or foe. In: Qian X, editor. *Glucocorticoids. New recognition of our familiar friend.* IntechOpen; 2012:569–592. ⁷⁸ Except fluticasone furoate, which was classified according to the Summary of Product Characteristics, based on indicated equivalence to fluticasone propionate. ^bEmitted doses.

Abbreviations: B, budesonide; BDP, beclomethasone dipropionate; FF, fluticasone furoate; FoF, formoterol fumarate; FP, formoterol fumarate; FP, fluticasone propionate; G, glycopyrronium; I, indacaterol; ICS, inhaled corticosteroids; S, salmeterol; T, tiotropium; U, umecidinium; V, vilanterol.

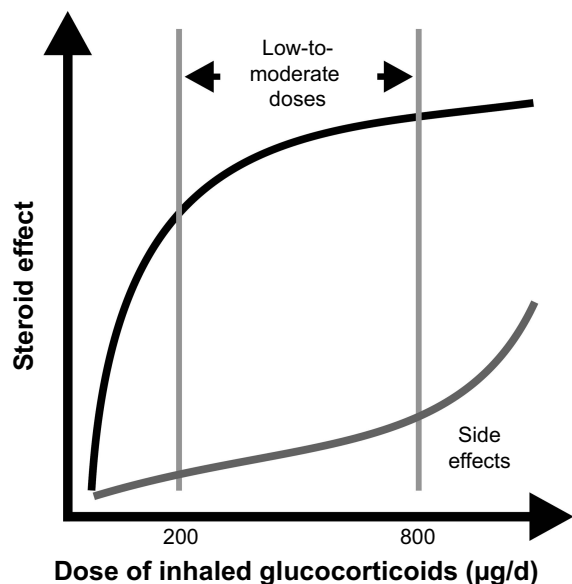


Figure 2 The dose-response curve of ICS.
Note: Reproduced from Kankaanranta et al, 2004,⁵⁶ with the permission of *Respiratory Research*.
Abbreviation: ICS, inhaled corticosteroids.

reduced airway bacterial load and reduced risk of pneumonia and tuberculosis.^{42,61} The mechanisms involved in systemic adverse effects of ICS are summarized in Figure 3. Taken into consideration the predominantly anti-inflammatory effects as well as low systemic exposure associated with lower ICS doses, the ICS dose reduction (rather than withdrawal) would be a plausible therapeutic option for many COPD patients.

Effects of ICS withdrawal

The effect of ICS withdrawal on lung function, symptoms, and exacerbations remains unclear, since the studies

published so far have provided conflicting results.⁶⁴⁻⁶⁸ Some studies have shown an increase in exacerbations and/or worsening of symptoms following ICS withdrawal, while others have not. A recent study conducted in 2,485 patients with moderate COPD has found no change in the incidence of exacerbations after ICS discontinuation, but a significant worsening in FEV₁ and quality of life was observed, instead.⁶⁴ Moreover, more detailed analysis from this study showed a significant increase in the incidence of severe exacerbations after ICS withdrawal and a heterogeneous response,⁶⁹ with a significant increase of exacerbations in those with blood eosinophil counts of $\geq 4\%$ or ≥ 300 cells/ μL .⁷⁰ Interestingly, although ICS in this study were discontinued gradually in three steps over a 12-week period, the worsening in FEV₁ became apparent only at the point of complete ICS withdrawal.⁷¹ This observation supports the hypothesis that using lower doses of ICS in COPD could be a better choice than their complete discontinuation. Intriguingly, there were no differences between the two arms in terms of pneumonia incidence, suggesting that ICS use was not associated with an increased pneumonia risk.⁷²

Another recent study has provided data on withdrawal of ICS in patients on long-term triple therapy in the absence of frequent exacerbations.⁷³ This 26-week, randomized, double-blind, triple-dummy study (SUNSET study) assessed the direct change from long-term triple therapy to indacaterol/glycopyrronium (110/50 μg once daily) or continuation of triple therapy (tiotropium [18 μg] once daily plus combination of salmeterol/fluticasone propionate [50/500 μg] twice daily). Primary endpoint was noninferiority on change from baseline in trough FEV₁. ICS withdrawal led to a reduction in

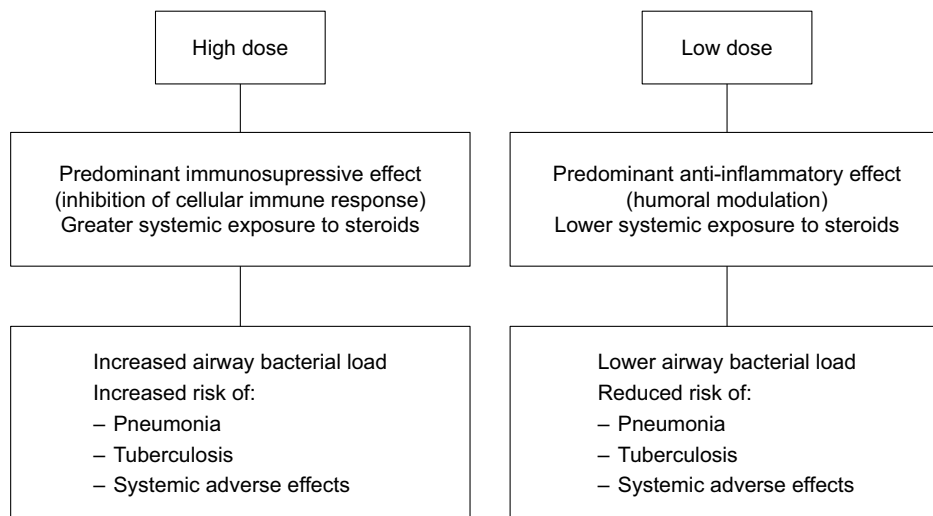


Figure 3 Pathophysiological mechanisms involved in systemic adverse effects of ICS in COPD patients.
Abbreviation: ICS, inhaled corticosteroids.

trough FEV₁ of -26 mL (95% CI: -53, 1 mL) with confidence limits exceeding the noninferiority margin of -50 mL. Differences in COPD exacerbations were not observed, although 26 weeks is not a sufficient time to assess differences in terms of exacerbations. Patients with ≥ 300 blood eosinophils/ μ L at baseline presented greater lung function loss and higher exacerbation risk, which suggests that these patients may obtain more benefit from triple therapy. Also, differences in quality of life (total score of the SGRQ) in favor of triple therapy were observed.

Finally, a post hoc pooled analysis of three randomized controlled trials of budesonide-formoterol in patients with COPD with a history of exacerbations and available blood eosinophil counts (INCONTROL study)⁷⁴ showed non-linear increase in exacerbations occurred with increasing eosinophil count in patients who received formoterol alone. Budesonide-formoterol compared with formoterol alone reduced the risk of exacerbation by 68% in patients with eosinophil count $\geq 0.6 \times 10^9$ /L. By contrast, in ex-smokers, budesonide-formoterol reduced the risk of exacerbations in only 34%–39% vs formoterol alone. The effect of treatment in ex-smokers was independent of the eosinophil count. These results suggest that in COPD patients who are active smokers, the eosinophil count may be a strong and independent predictor of future exacerbations.

Concluding remarks

Inhaled steroids in combination with long-acting bronchodilators have become a standard treatment strategy for COPD, especially in patients suffering from frequent exacerbations and in those with mixed asthma-COPD phenotype. Increased risk of pneumonia and systemic adverse effects of ICS have generated a debate around their long-term use, in particular, for high doses of ICS. The safety profile of ICS seems to be dose dependent and most serious adverse events have been related to the use of high doses (eg, fluticasone propionate 1,000 μ g/day), with a reduced risk when lower doses are given. The relatively flat dose-response curve explains the little clinical benefit derived from increasing ICS dose above minimally effective doses, whereas the risk of adverse events is increased, coinciding with the steeper part of the dose-response curve for systemic effects. Also, differences in physiopathological mechanisms underlying the action of ICS, predominantly immunosuppressive at high doses and anti-inflammatory at lower doses, further support the strategy of using lower ICS doses. These considerations highlight the value of using low-dose ICS in the management of COPD.

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