Step down or therapeutic re-organization approach for withdrawal of inhaled corticosteroids in selected patients with COPD? A proposal for COPD management

Authors:

Claudio Micheletto [1], Fulvio Braido [2], Marco Contoli [3], Fabiano Di Marco [4], Pierachille Santus [5]

Affiliations:

[1] Respiratory Unit, Azienda Ospedaliera Universitaria Integrata, Verona Italy.
2 Department of Internal Medicine, Respiratory Diseases and Allergy Clinic, University of Genova, Azienda Policlinico IRCCS San Martino, Genoa, Italy.
3 Department of Medical Sciences, University of Ferrara, Ferrara, Italy.
4 Department of Health Sciences, Università degli Studi di Milano. Respiratory Unit, Papa Giovanni XXIII Hospital, Bergamo, Italy.
5 Department of Health Sciences, Università degli Studi di Milano. Pulmonary Unit, Luigi Sacco University Hospital, ASST Fatebenefratelli, Milan, Italy.

Correspondence:

Claudio Micheletto
Respiratory Unit, Azienda Ospedaliera Universitaria Integrata, Piazzale Stefani 1, 37122 Verona Italy
+39 0458122248
claudio.micheletto@univr.it

Target journal: Int J Chron Obstruct Pulmon Dis

Abstract

While chronic obstructive pulmonary disease (COPD) continues to be a major cause of morbidity and mortality, pharmacological therapy has a definite benefit on symptoms, frequency and severity of exacerbations, and general health status. The most recent Global Initiative for Obstructive Lung Disease (GOLD) guidelines recommend triple therapy (long-acting beta2 agonists [LABA] + long-acting muscarinic antagonists [LAMA] + inhaled corticosteroids [ICS]) only for patients with exacerbations, elevated eosinophils, and without control using a LABA/LAMA or ICS/LABA combination. Long-term monotherapy with ICS is not recommended, but may be considered in association with LABAs in patients with a history of exacerbations and elevated eosinophils in spite of appropriate treatment with long-acting bronchodilators. However, long-term use of ICS in combination therapy has been associated with adverse effects, even if widely used in routine management for decades. The available evidence suggests that ICS can be rationally withdrawn in patients with stable disease and is not likely to have unfavorable effects on lung function, overall health, or be associated with a greater risk of exacerbations. Indeed, it is widely accepted that ICS therapy should be limited to a minority of patients after careful assessment of the individual risk-benefit profile. Unfortunately, however, there are no international recommendations that provide specific guidance or a protocol for withdrawal of ICS. Herein, the available evidence on the use of ICS is reviewed and an easy to use tool is proposed that can provide clinicians with a simple management scheme to guide the most appropriate therapy for management of COPD and use of ICS. In management of COPD, a highly personalized approach is advocated in order to select the most appropriate therapy for each individual patient.

Keywords: COPD, exacerbation, inhaled corticosteroids, LABA, LAMA

Introduction

Despite advances in therapy, chronic obstructive pulmonary disease (COPD) remains a leading cause of both morbidity and mortality [1,2]. Pharmacological therapy for COPD has a definite positive impact on the disease as it can improve symptoms and the frequency and severity of exacerbations, while ameliorating exercise tolerance and general health status [3]. At present, the main options for management of COPD include a relatively small number of drug classes, namely bronchodilators (short- and long-acting beta2 agonists [SABAs, and LABAs], short- and long-acting muscarinic antagonists [SAMAs, and LAMAs]), along with inhaled corticosteroids (ICSs) and inhibitors of PDE-4. Control of exacerbations are important since severe COPD exacerbations have both short- and long-term implications, may negatively affect lung function, and have been associated with increased mortality and cardiovascular complications, with obvious implications for higher costs of care [4-6].

The main goals of therapy for COPD are prevention and control of symptoms, diminish both frequency and severity of exacerbations, and improve exercise tolerance to improve the overall quality of life. Long-acting bronchodilator monotherapy is known to increase lung function and patient-reported outcomes such as symptoms and quality of life, enhance exercise performance, and reduce exacerbations [7,8]. Concomitant administration of LABA/LAMA significantly improves lung function vs. a single bronchodilator [9]. The SPARK trial showed that fixed combination indacaterol plus glycopyrronium (IND/GLY) was superior in preventing moderate to severe COPD exacerbations compared to monotherapy with the long- acting anti-muscarinic bronchodilator glycopyrronium alone [10]. It is believed that the additive effects commonly observed by the combination invokes the different mechanisms of action of beta-2 agonists and muscarinic antagonists with possible intracellular interactions between the two pathways [11]. Moreover, there is increasing evidence that long-term treatment with a combination inhaler containing ICS/LABA is more effective than the individual components in improving lung function and reducing the frequency of exacerbations [12].

The most recent update of the Global Initiative for Obstructive Lung Disease (GOLD) recommends triple therapy (ICS + LABA + LAMA) only for patients with exacerbations and

elevated eosinophil levels who are not controlled with a LABA/LAMA or ICS/LABA combination [3]. Given that the components of triple therapy have different mechanisms of action, this provides a strong rationale for the concomitant use of these drugs to optimize the prevention of exacerbation and potential clinical benefits according to pivotal studies [13,14]. Today, triple therapy is widely prescribed in clinical practice. According to a recent review on general practice in the UK, the use of triple therapy increased from 25% to 59% in patients with very severe COPD over the period from 2004 to 2009 [15]. Moreover, a real-world study in Italy showed that 6.3% of newly-diagnosed patients were being treated with triple inhaled therapy with ICSs, and that 42% of these patients initiated triple therapy at diagnosis; in that study, older male gender and prescription of ICS/LABA FDC at the time of diagnosis appeared to be the strongest predictors for prescription of triple therapy [16]. In support of such a strategy, a recent systematic review and meta-analysis concluded that triple therapy is associated with a lower rate of moderate or severe exacerbations of COPD, and improved lung function, as well as better health related quality of life compared to monotherapy or dual therapy [17].

Recently, the TRIBUTE study assessed 1532 patients who were receiving inhaled maintenance medication and had symptomatic COPD, severe or very severe airflow limitation and at least one moderate or severe exacerbation in the previous year and randomized to a single-inhaler triple combination of beclometasone dipropionate, formoterol fumarate, and glycopyrronium (BDP/FF/G) or a single-inhaler dual bronchodilator combination of IND/GLY [18]. The primary endpoint was rate of moderate-to-severe COPD exacerbations over 52 weeks of treatment. In these patients, an extrafine formulation of BDP/FF/G significantly reduced the rate of moderate-to-severe exacerbations compared with IND/GLY, and did not increase the risk of developing pneumonia.

In response to a letter to the editor, the authors provided additional data on the distribution of patients by exacerbation rates in TRIBUTE in the BDP/FF/G and IND/GLY treatment arms [19]. The data showed that the difference between the two treatments was only present in patients with ≥ 3 exacerbations. Thus, it can easily be derived that patients with ≤ 2 exacerbations, who were ~95% of the study population, benefited from double bronchodilation without the need of ICS and only about 5% of patients with ≥3 exacerbations, or “super

exacerbators", would potentially benefit from triple combination therapy, which is consistent with data from other studies such as Sunset [20]. Indeed, the number of patients with ≥1 exacerbations was 273 with BDP/FF/G vs 288 with IND/GLY, for a difference of only 15 exacerbations in more than 1500 patients; the incidence of COPD exacerbations was low in both study arms, suggesting that both treatments were effective in reducing the rate of COPD exacerbations (Table 1).

In the current GOLD recommendations, it is acknowledged that there is a lack of high-quality evidence supporting initial strategies for pharmacological treatment in newly diagnosed patients with COPD [3]. In the 2019 GOLD update, ICS are now recommended as first choice only for some patients belonging to GOLD group D, and only in combination with LABAs (Figure 1) [3]. Long-term monotherapy with ICS is not recommended, but may be considered in association with LABAs in patients who have a history of exacerbations and elevated eosinophils in spite of appropriate treatment with long-acting bronchodilators [3]. However, it is worthwhile noting that long-term use of ICS in either dual or triple therapy has been associated with some complications and adverse effects [18,21,22], even if they are widely used in routine management of patients for many years. As also stated in the GOLD guidelines, ICS may increase the risk of side effects such as pneumonia [3]. Thus, there remains on-going concern over the long-term use of ICS, despite their recommend use in combination with long-acting bronchodilators for patients who are at risk of exacerbations. Indeed, ICS are still routinely prescribed to the majority of patients with COPD at high risk of exacerbations and elevated eosinophils, even if GOLD criteria for their administration are not met [23,24].

Patient phenotypes and ICS withdrawal

Given the wide range of COPD patient phenotypes and clinical presentations, with potentially diverse pathophysiological mechanisms, it is not likely that all patient subtypes will benefit from ICS, which may in part explain some of the discrepant results in the literature. There is, in fact, increasing evidence that patients with some phenotypes may benefit more than others from the addition of ICS to treatment regimens. In particular, it appears likely that those

with asthma–COPD overlap (ACO), frequent exacerbators, and those with eosinophilic inflammation may benefit most from ICS.

Asthma–COPD overlap

Although its prevalence is difficult to estimate, roughly one-fourth of patients with COPD may be considered to have ACO in which some feature of asthma and COPD coexist without presenting as a distinct syndrome [25]. In a large analysis of over 5500 patients, among older individuals with COPD and asthma newly prescribed LABA and ICS combination therapy was associated with a significantly lower risk of death or COPD hospitalization vs. newly prescribed LABAs alone [26]. Real-world practice seems to confirm this, as only 18% of patients with ACO are not routinely prescribed an ICS [27]. Lee et al. have also provided clinical evidence that ACO patients having mild-to-moderate airflow limitation will show a greater response in lung function after treatment with an ICS/LABA combination after 3 months [28]. Of note, in a database study of over 250,000 patients with ACO in Taiwan, use of LAMA or an ICS/LABA combination was found to be associated with a lower risk of acute exacerbation [29]. Expert opinion seems to suggest that for patients who do not have ACO, LAMA/LABA may be appropriate for initiating therapy, while those who still have exacerbations may require additional drug therapy, such as ICS or PDE-4 inhibitors, taking into consideration the risk-benefit ratio in individual patients [30].

Frequent exacerbators

Frequent exacerbators are another well-represented subclass of patients with COPD. The risk of exacerbation is normally based on either GOLD classification of airway limitation or history of exacerbations (i.e., high risk is defined as $\geq$2 exacerbations or $\geq$1 hospitalization per year). Even considering this definition, many patients with moderate-to-severe COPD, or those classified as GOLD stage C and D, are not frequent exacerbators, and thus do not meet qualifications for ICS therapy [25].

Recently, Le Rouzic and colleagues prospectively recorded the number of moderate and severe COPD exacerbations in 835 current and former smokers with GOLD stage 2-4

disease for 4 years [31]. The authors found that the 464 participants followed for the full 4 years consistently fit into two distinct clusters. The first was characterized by a relatively low exacerbation frequency (0.71 ± 0.54 exacerbation/subject/year) and comprised 75% of participants; the second cluster was defined by participants with more frequent exacerbations (2.89 ± 1.07 exacerbations/subject/year). An extended analysis involving 608 participants with at least 2 years of follow-up resulted in similar clusters. Of note, only 7% of the subjects followed for the total duration of the study had two or more exacerbations per year during each of the 4 years.

Current GOLD recommendations are somewhat based on the 26-week ILLUMINATE trial in 523 patients with moderate-to-severe COPD and no history of exacerbations, which reported significantly greater clinical improvement in lung function and clinical benefit with once-daily IND/GLY than salmeterol + fluticasone [32]. Additionally, the more recent ENERGITO trial further substantiated that in patients with moderate-to-severe COPD once-daily tiotropium + olodaterol showed superior benefits in lung function to twice-daily salmeterol + fluticasone [33]. Lastly, while history of exacerbations and severity of COPD are undoubtedly risk factors for recurrent exacerbations, it seems clear that other risk factors associated with exacerbations must also be taken into consideration, which include eosinophilic inflammation, common comorbidities such as cardiovascular disease, psychiatric comorbidities, and advanced age. Moreover, to further complicate this issue, it has recently been suggested that each common medication usage group for COPD may have unique risk factor patterns that are associated with increased risk of exacerbations [34]. For example, despite similar baseline characteristics, tiotropium users appear to show lower rates of exacerbations (OR = 0.69, p = 0.09) than ICS ± LABA users, especially in those without comorbid asthma (OR = 0.56, p = 0.05). In support of the concept of an activity for tiotropium that is not related to bronchodilation, in COPD patients the drug has been associated with a more favorable anti-inflammatory profile than formoterol as it reduces production of superoxides and leukotriene B_4 by peripheral neutrophils [35].

Eosinophilic inflammation

Several studies have demonstrated a relation between airway eosinophilia and exacerbations of both chronic bronchitis and COPD [36-39] In addition, an association between sputum eosinophilia and steroid responsiveness in COPD has been noted [40,41]. In patients with acute exacerbations of COPD, the administration of systemic corticosteroids has shown superior benefit in patients with a blood eosinophil level of ≥2% compared with those having a level <2% [42,43]. In this regard, two post-hoc analyses in patients with moderate-to-very severe COPD reported greater reduction of moderate and severe exacerbations in patients with blood eosinophil level ≥2% than in those with <2% if undergoing treatment with fluticasone furoate/vilanterol compared with vilanterol alone [44,45]. Analysis of the data in these trials has strongly suggested that baseline blood eosinophil levels may therefore represent a valid marker for reduction of exacerbation with ICS/LABA in patients with COPD and clinical history of moderate/severe exacerbations, as confirmed in a recent review [46].

A post hoc analysis of randomized, double-blind, parallel-group FORWARD trial concluded that greater reduction in exacerbations was observed when ICS was added to a LABA in patients with severe COPD and a history of exacerbations with eosinophil count ≥279.8 cells/mm^3 [47]. The Copenhagen General Population Study on 7,225 patients with COPD over median follow-up of 3.3 years used an absolute cut-off, and reported that absolute blood eosinophil count of ≥340 cells/mm^3 was able to predict the risk of both moderate and severe exacerbation vs a cut-off of 2% [48]. Based on these results, ≥300 cells/mm^3 can be used as a provisional cut-off until further information is made available. However, clinicians must also consider that blood eosinophil counts are easily measured and more accessible than levels of eosinophils in sputum. Use of blood eosinophil counts as a biomarker of ICS response can also lead to greater overall improvement of lung function, increased quality of life, and decreased frequency of exacerbation in patients with COPD with blood eosinophil counts >3%, especially when treated with a higher dose of ICS [49]. The meta-analysis by Cazzola reported that patients who still have exacerbations and have blood eosinophil count ≥300 cells/µl on single long-acting bronchodilator therapy or a LABA/LAMA combination might benefit from LABA/LAMA + ICS [52]. In that analysis, the risk of pneumonia did not significantly differ between ICS/LABA/LAMA and

comparators [52]. However, long-term treatment with ICS is known to affect bacterial load in patients with stable COPD, and lower eosinophil levels are related to increased bacterial load of the airways [53]. In fact, an inverse relationship between bacterial infection and eosinophil counts has been documented; bacterial infection thus has the possibility to alter responsiveness to ICS by neutrophilic and eosinophilic inflammation [54]. In short, high blood levels of eosinophils can help predict future exacerbations, and may predict a more favorable response to ICS when added to LABA/LAMA, particularly so in patients with a history of frequent exacerbations, even if additional studies are still needed [50,51].

ICS withdrawal: clinical evidence

As noted in the review by Kaplan, despite the introduction of ICS into clinical practice over 2 decades ago, the option to continue or withdraw ICS in patients with COPD remains somewhat unsubstantiated, with conflicting evidence [55]. The "step down" approach does not historically apply to COPD, but the excessive and inappropriate use of ICS in COPD, together with the increased risk of associated adverse effects such as pneumonia, renders it necessary to discontinue ICS in patients in whom the risks overweight the possible benefits. In fact, the superiority of ICS/LABA combinations compared to LABA alone in preventing exacerbations were strongly disputed in a Cochrane meta-analysis several years ago [56]. In 2017, Calzetta carried out a meta-analysis in withdrawal of inhaled corticosteroids in COPD wherein it was reported that withdrawal of ICS did not significantly increase the overall rate of COPD exacerbations, even if an increased, clinically-relevant risk of severe exacerbation was seen (RR >1.2) [57]. Moreover, ICS withdrawal significantly impaired both lung function and quality of life, with a significantly shorter time to first exacerbation in those who withdrew from ICS.

In the INSTEAD (Indacaterol: Switching Non-exacerbating Patients with Moderate COPD from Salmeterol/Fluticasone to Indacaterol) trial, no clinically relevant reductions in lung function were seen during 26 weeks in patients who switched to indacaterol vs. those who continued fluticasone/salmeterol therapy [58]. Furthermore, in this study, the annual rate of all COPD exacerbations showed no significant difference between groups, and the trial concluded that patients with moderate airflow limitation and no history of exacerbations can be switched

from fluticasone/salmeterol to indacaterol monotherapy with no compromise in terms of loss in efficacy. A recent study from The Netherlands reported that ICS discontinuation increases airway inflammation in patients with moderate-severe COPD, which suggests that the potential anti-inflammatory effects of ICS are not maintained after discontinuation of ICS [59].

At least three studies have examined the effects of ICS withdrawal in real-life settings. In the first, OPTIMO, the risk of exacerbations did not significantly increase over 6 months after ICS withdrawal when compared with continued ICS/bronchodilator therapy, with no evidence of deterioration in either symptoms of COPD or lung function over a 6 month period following withdrawal of ICS [60]. In agreement with this possibility, the prospective, non-interventional 2-year DACCORD study from Germany studied the consequences of ICS withdrawal in 236 of 1022 patients with COPD [61]. Patients in whom ICS was withdrawn showed shorter disease duration and better lung function, with 74.2% of patients in whom ICS was withdrawn not exacerbating, compared with 70.7% among those who continued ICS; over the first year, exacerbation rates were 0.414 in the withdrawal group and 0.433 in those who continued ICS. These real-life data thus add to the continuing controversy in patients with COPD managed in primary and secondary care.

Chapman et al. reported the results of a 6-month ICS withdrawal trial in 1053 COPD patients without a history of frequent exacerbations or asthma who had nonetheless been receiving triple therapy as part of routine care during the previous > 6 months [20]. After a 4-week run-in period on a triple combination of tiotropium, salmeterol, and fluticasone propionate, the ICS was abruptly withdrawn in double-blind, triple-dummy fashion in a random half of patients who were switched at the same time a dual bronchodilator in a single inhaler (IND/GLY), while the other half remained on the same triple regimen. ICS withdrawal led to a modest, statistically non-significant decline in FEV_1 of 26 ml on average mainly during the first 4 weeks after abrupt withdrawal, no increase in exacerbation rate, and a small, non-significant worsening of quality of life. The declines in FEV_1 after ICS withdrawal were noted predominantly in the ex-smoker subgroup.

Interestingly, the WISDOM trial has studied the effects of ICS withdrawal on blood eosinophil count and exacerbations [62]. Among the 2296 patients who received treatment

following ICS withdrawal, the rate of moderate or severe exacerbations was the same in the overall population but higher in the ICS-withdrawal group compared with the ICS-continuation group in patients with eosinophil counts ≥2% (RR 1.22; [95% CI 1.02-1.48]), ≥4% (RR 1.63; [1.19-2.24]) or ≥5% (RR 1.82; [1.20-2.76]). Thus, the increase in rate of exacerbations increased as the eosinophil cut-off level increased. Interestingly, another analysis of the same study showed that only patients with more than 2 exacerbations in the previous year and blood eosinophil above 300 cells/μL showed a significantly increased risk of exacerbations after ICS withdrawal.

AFFIRM COPD (Aclidinium and Formoterol Findings in Respiratory Medicine COPD) randomized 933 patients with moderate-to-severe COPD to aclidinium/formoterol twice daily or salmeterol/fluticasone twice daily over 24 weeks [63]. Aclidinium/formoterol showed superiority over salmeterol/fluticasone in terms of lung function measured as FEV1, with a mean improvement of 93 mL for the LAMA/LABA treatment compared with salmeterol/fluticasone. However, there was no difference between the two groups in terms of exacerbations and patient-reported outcomes such as dyspnea and quality of life [63].

The recent FLAME trial directly compared LABA/LAMA to the ICS/LABA combination [64]. In this large 52-week study, 3360 patients with moderate-to-severe COPD were randomly assigned to either a twice-daily fixed-dose combination of salmeterol and fluticasone or the once-daily fixed combination of IND/GLY, both on a maintenance basis. Patients who received IND/GLY experienced an 11% lower risk of all COPD exacerbations at 1 year compared with patients who received salmeterol-fluticasone. The IND/GLY group had a longer time to first exacerbation than the salmeterol-fluticasone group (71 days vs. 51 days) representing a 16% lower risk ($p<0.001$), a lower annual rate of moderate or severe exacerbations, and longer time to the first moderate or severe exacerbation. Thus, IND/GLY was more effective than salmeterol-fluticasone in preventing exacerbations of COPD in patients with a history of exacerbation during the previous year. Moreover, the effect of IND/GLY on COPD exacerbations compared to salmeterol-fluticasone was independent of the baseline blood eosinophil count.

In a post hoc analysis of FLAME, IND/GLY provided greater or comparable exacerbation prevention than salmeterol-fluticasone in all groups when stratified by eosinophil levels and exacerbation history, further supporting the use of IND/GLY to prevent exacerbation in moderate-to-very severe COPD [65]. Considering the value of eosinophils as a predictor of responsiveness to the combination of ICS/LABA, a prospective analysis of data from FLAME reported that IND/GLY has superior or similar benefits over salmeterol/fluticasone independently of blood eosinophil levels [66]. Lastly, a subgroup analysis of the FLAME study validated the consistent beneficial effects of IND/GLY compared to salmeterol-fluticasone on moderate/severe exacerbations that was independent of either history of prior exacerbation or treatment [67].

Beyond FLAME

While the landmark trial FLAME trial showed greater reduction in exacerbations with LABA/LAMA than LABA/ICS in symptomatic patients with a history of exacerbations, an analysis of this trial has suggested that prevention of exacerbations with IND/GLY was similar or possibly superior to that with salmeterol-fluticasone for all ranges of blood eosinophil levels [66]. This is in contrast to a post-hoc analysis of WISDOM, which suggested that at least some patients, namely those with a history of exacerbations and high eosinophil levels, are at increased risk of exacerbations after withdrawal of ICS [68]. Another more recent post-hoc analysis of the FLAME study evaluated the effects of treatment on moderate/severe exacerbations based on absolute blood eosinophil count (cut-offs of 150 and 300 cells/μL) and percentage (2%, 3%, and 4%), as well as exacerbation history (1 exacerbation and ≥2 exacerbations) [69]. In patients with <150 cells/μL, IND/GLY significantly reduced the rate of moderate/severe exacerbations vs. salmeterol-fluticasone in patients with 1 and ≥2 exacerbations, and the effects of both treatments were comparable in patients with ≥150 cells/μL and ≥300 cells/μL, independent of history of exacerbation. IND/GLY was always superior in patients with low blood eosinophils, but of similar efficacy in the higher eosinophil groups, providing further evidence that blood eosinophils may help to identify patients who will benefit from ICS in addition to LABA/LAMA. The results of this post-hoc analysis give further

support the efficacy of IND/GLY for prevention of exacerbations in patients with moderate-to-severe COPD, and particularly in individuals who are at higher risk of exacerbations, further confirming the validity of the current GOLD recommendations regarding LABA/LAMA over LABA/ICS in COPD patients who are at risk of exacerbations [25].

Guidelines on ICS use in COPD

Unfortunately, at present, there are no international guidelines that recommend how to perform withdrawal of ICS or provide a protocol for withdrawal when deemed necessary by the clinician; as the available data are not conclusive, more studies are needed to further understand in which patients withdrawal of ICS can be considered to be safe and beneficial.

In a 2015 Spanish consensus document, it was agreed that ICS therapy should be added to long-acting bronchodilators in patients with frequent exacerbations and in those with ACOS, although it should not be added to LABA therapy in order to improve lung function [70]. Moreover, these experts further agreed that ICS withdrawal in patients with stable COPD was indeed possible, but with no consensus reached on how, when, or in which patients to discontinue ICS. Recommendations were mostly limited to stating that withdrawal of ICS in COPD is feasible, that those who discontinue ICS should be monitored in the short-term, and that withdrawal of ICS should be tapered. Following changes to the GOLD document in 2017, in which impaired lung function is no longer considered as a determinant for risk of exacerbation, many COPD patients can now be considered to belong to group B, with a low risk of exacerbations and high level of symptoms [25], and some considerations have been made in this regard [71].

Previous authors have attempted to provide algorithms for withdrawal of ICS in patients with COPD [55]. The algorithm proposed by Kaplan takes into consideration exacerbation risk, according to GOLD, but also the emergent ACOS phenotype, as per the GINA/GOLD Consensus Statement. The algorithm further considers potential markers of eosinophilia, with a stepwise withdrawal protocol using dual bronchodilation that is mainly based on the WISDOM trial. Briefly, the algorithm consists of 5 steps in which current management is reviewed and the risk-benefits of continuing ICS therapy are assessed, considering ACO, frequency of

exacerbations, and other potential markers such as eosinophils (sputum ≥3%, blood eosinophils ≥300 cells/μL). A decision is then made to withdraw (or not) ICS therapy. If withdrawn, a stepwise approach is taken, with possible step-up and step-down of ICS doses. Bronchodilation therapy with LABA/LAMA is optimized, and patients are followed regularly every 3 months. While oversimplified in the present discussion, other authors have held that such a proposal is somewhat complex and difficult to adopt in daily clinical practice [72].

As such, other algorithms have been recently developed. The first is a simple dyspnea-based treatment algorithm for inhaled pharmacotherapy of COPD [73]. Patients are subgrouped based on the presence of low (<2 mMRC dyspnea scale) or high (≥2 mMRC dyspnea scale) dyspnea. If the patient has a low score, one long-acting bronchodilator is given, while two bronchodilators are given if the patient has a high score. In the presence of ≥2 exacerbations in the previous year (keeping in mind that even a patient with one severe exacerbation and hospitalization is considered a frequent exacerbator), ICS are added to treatment, independently of the degree of dyspnea. The algorithm was also validated on 100 patients in primary and tertiary care.

In a second simplified algorithm proposal, the decision to withdraw or continue ICS is initially based on stratification for the presence of ACO [72]. In patients with FEV1 > 50% and no previous exacerbations, ICS should be withdrawn. In patients with ACO and exacerbations in the previous year, the risks associated with ICS withdrawal exceed the benefits and ICS should not be withdrawn. Patients with FEV1 > 50% and exacerbations in the previous year as well as those with FEV1 < 50% without exacerbations should be carefully evaluated for withdrawal of ICS. As such, dual bronchodilator therapy should be maintained to make sure that the risk of exacerbations does not increase in these subgroups. In patients with FEV1 < 50% and exacerbations in the previous year, together with patients with ACO without exacerbations, discontinuation of ICS should only be considered in patients with a significant risk of serious ICS-related side effects. Close follow-up is essential.

Conclusions for daily practice

In line with current clinical practice guidelines for COPD, the addition of ICS to long-acting β2 agonist therapy is recommended only in patients with moderate-to-severe disease who are at increased risk for exacerbations, although fixed-dose combinations of ICS/LABA are often used against current guideline recommendations in patients at a low exacerbation risk. The available evidence from controlled trials adds weight to the hypothesis that ICS can be reasonably discontinued, from both safety and efficacy standpoints, in patients with stable COPD and in those for whom ICS therapy may not be indicated; in the majority of patients, discontinuation is not likely to have detrimental effects on lung function, overall health status, or lead to a greater risk of exacerbations. Due to the lack of international guidelines, several groups have proposed algorithms for withdrawal of ICS in patients with COPD. While the complexity of these algorithms may differ, all adhere to the principles of the most recent GOLD guidelines, even if their solid validation remains a weak point for their implementation. Nonetheless, all are also based on the underlying principle that ICS therapy is associated with an increased risk of potentially serious adverse effects and complications, and as such, its use should be limited to a minority of patients after careful evaluation of the individual risk-benefit profile. Following ICS withdrawal, patients should be maintained on dual bronchodilator therapy and carefully followed. Moreover, ICS therapy may be discontinued either abruptly or via gradual dose reduction in a stepwise fashion, but in any case close monitoring is essential. Patients should not experience a decline in lung function during withdrawal. Particular care is warranted in high-risk patients with frequent exacerbations or in those with poor lung function and taking high doses of ICS. This is especially true when considering initiating a patient on ICS therapy or the safe discontinuation of ICS in patients who are already on long-term therapy. While promising, the role of elevated blood eosinophils as a marker to identify identification of candidates for ICS treatment is currently debated, and further clinical studies are needed. Indeed, the available data support a role for ICS in the presence of eosinophil levels ≥300 cells/μL. In the absence of unequivocal guidance, clinicians should continue to carefully evaluate and treat patients on an individual basis.

Future directions

The GOLD 2019 strategy proposed a model for the initiation of pharmacological management of COPD according to individualized assessment of symptoms and exacerbations; ICS are only recommended as first choice in some GOLD D patients with particular characteristics such as high blood eosinophil counts ≥ 300 cells/μL (in treatment naïve patients) or history of asthma [3] (Fig. 1). This recommendation anyway comes together with the alert of possible development of pneumonia, so that ICS should be used as initial therapy only after the possible clinical benefits versus risks have been considered. The current GOLD 2019 strategy recommends a 3-step review for assessment and adjustment for which escalation or switching inhaler device or molecules within the same class may be considered as appropriate. The response to treatment escalation should always be reviewed, and de-escalation should be considered if there is a lack of clinical benefit and/or side effects occur. De-escalation may also be considered in COPD patients receiving treatment who return with resolution of some symptoms that subsequently may require less therapy, this should be undertaken under close medical supervision. ICS withdrawal is currently recommended in COPD patients who experience adverse effects from ICS treatment as well as patients with inappropriate ICS treatment or those not showing benefits from the same treatment. Unfortunately, GOLD recommendations do not provide any suggestion on how to do this withdrawal (abruptly or with ICS dose tapering, even if off-label) and what phenotype of patients should be considered for this therapeutic re-organization. In this regard, one might consider ICS withdrawal in those with low eosinophil counts, no ACO, or ICS-related adverse events.

Interestingly, the IPCRG group has recently issued an algorithm for ICS withdrawal by simply assessing if the patient has asthma features or high exacerbation risk, and gives recommendations on the possibility to continue ICS treatment or to re-organize COPD maintenance treatment in favor of a double bronchodilator treatment (with no ICS added) [74]. In this context an easy tool that gives physicians a support to guide the most appropriate COPD management seems particularly useful (Fig. 2). The question of if not needed “the ICS should be abruptly withdrawn or the dose should be reduced gradually until full withdrawal” has no strong evidence based answer at this time. What is important is the acknowledgement of a need to re-evaluate treatment for all COPD patients and in light of the ancient principle “first do not

harm” any unnecessary or potentially harmful treatment should be withdrawn, to put in practice the therapeutic re-organization that aims to a personalized medicine that is currently quite far from COPD management in routine clinical practice.

Acknowledgements

Editorial assistance for the manuscript was provided by Dr. Patrick Moore, on behalf of Health Publishing & Services srl and supported by an unrestricted grant from Novartis Farma Italy.

Disclosure

The authors report no conflicts of interest in this work. Dr. Moore declares there are no potential conflicts of interest relating to his editorial assistance.

References

1. Lopez AD, Shibuya K, Rao C, et al. Chronic obstructive pulmonary disease: current burden and future projections. *Eur Respir J.* 2006;27(2):397-412.
2. Mathers CD, Loncar D. Projections of global mortality and burden of disease from 2002 to 2030. *PLoS Med.* 2006;3(11):e442.
3. Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2019 Report. Available at: https://goldcopd.org.
4. Chenna PR, Mannino DM. Outcomes of severe COPD exacerbations requiring hospitalization. *Semin Respir Crit Care Med.* 2010;31(3):286-294.
5. Halpin DM, Decramer M, Celli B, Kesten S, Liu D, Tashkin DP. Exacerbation frequency and course of COPD. *Int J Chron Obstruct Pulmon Dis.* 2012;7:653-661.
6. Toy EL, Gallagher KF, Stanley EL, Swensen AR, Duh MS. The economic impact of exacerbations of chronic obstructive pulmonary disease and exacerbation definition: a review. *COPD.* 2010;7(3):214-228.
7. Kew KM, Dias S, Cates CJ. Long-acting inhaled therapy (beta-agonists, anticholinergics and steroids) for COPD: a network meta-analysis. *Cochrane Database Syst Rev.* 2014(3):CD010844.
8. Ohar JA, Donohue JF. Mono- and combination therapy of long-acting bronchodilators and inhaled corticosteroids in advanced COPD. *Semin Respir Crit Care Med.* 2010;31(3):321-333.
9. Vincken W, Aumann J, Chen H, Henley M, McBryan D, Goyal P. Efficacy and safety of coadministration of once-daily indacaterol and glycopyrronium versus indacaterol alone in COPD patients: the GLOW6 study. *Int J Chron Obstruct Pulmon Dis.* 2014;9:215-228.
10. Wedzicha JA, Decramer M, Ficker JH, et al. Analysis of chronic obstructive pulmonary disease exacerbations with the dual bronchodilator QVA149 compared with glycopyrronium and tiotropium (SPARK): a randomised, double-blind, parallel-group study. *Lancet Respir Med.* 2013;1(3):199-209.

11. Cazzola M, Molimard M. The scientific rationale for combining long-acting beta2-agonists and muscarinic antagonists in COPD. *Pulm Pharmacol Ther.* 2010;23(4):257-267.
12. Ariel A, Altraja A, Belevskiy A, et al. Inhaled therapies in patients with moderate COPD in clinical practice: current thinking. *Int J Chron Obstruct Pulmon Dis.* 2018;13:45-56.
13. Cazzola M, Di Marco F, Santus P, et al. The pharmacodynamic effects of single inhaled doses of formoterol, tiotropium and their combination in patients with COPD. *Pulm Pharmacol Ther.* 2004;17(1):35-39.
14. van Noord JA, Aumann JL, Janssens E, et al. Comparison of tiotropium once daily, formoterol twice daily and both combined once daily in patients with COPD. *Eur Respir J.* 2005;26(2):214-222.
15. James GD, Donaldson GC, Wedzicha JA, Nazareth I. Trends in management and outcomes of COPD patients in primary care, 2000-2009: a retrospective cohort study. *NPJ Prim Care Respir Med.* 2014;24:14015.
16. Di Marco F, Santus P, Terraneo S, et al. Characteristics of newly diagnosed COPD patients treated with triple inhaled therapy by general practitioners: a real world Italian study. *NPJ Prim Care Respir Med.* 2017;27(1):51.
17. Zheng Y, Zhu J, Liu Y, et al. Triple therapy in the management of chronic obstructive pulmonary disease: systematic review and meta-analysis. *BMJ.* 2018;363:k4388.
18. Papi A, Vestbo J, Fabbri L, et al. Extrafine inhaled triple therapy versus dual bronchodilator therapy in chronic obstructive pulmonary disease (TRIBUTE): a double-blind, parallel group, randomised controlled trial. *Lancet.* 2018;391(10125):1076-1084.
19. Papi A, Singh D, Petruzzelli S, Guasconi A, Vestbo J. Inhaled triple therapy in chronic obstructive pulmonary disease - Authors' reply. *Lancet.* 2018;392(10153):1113-1114.
20. Chapman KR, Hurst JR, Frent SM, et al. Long-Term Triple Therapy De-escalation to Indacaterol/Glycopyrronium in Patients with Chronic Obstructive Pulmonary Disease (SUNSET): A Randomized, Double-Blind, Triple-Dummy Clinical Trial. *Am J Respir Crit Care Med.* 2018;198(3):329-339.

21. Calverley PMA, Stockley RA, Seemungal TAR, et al. Reported pneumonia in patients with COPD: findings from the INSPIRE study. *Chest.* 2011;139(3):505-512.

22. Price D, Yawn B, Brusselle G, Rossi A. Risk-to-benefit ratio of inhaled corticosteroids in patients with COPD. *Prim Care Respir J.* 2013;22(1):92-100.

23. Suissa S, Barnes PJ. Inhaled corticosteroids in COPD: the case against. *Eur Respir J.* 2009;34(1):13-16.

24. Vestbo J, Vogelmeier C, Small M, Higgins V. Understanding the GOLD 2011 Strategy as applied to a real-world COPD population. *Respir Med.* 2014;108(5):729-736.

25. Vogelmeier CF, Criner GJ, Martinez FJ, et al. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Lung Disease 2017 Report. GOLD Executive Summary. *Am J Respir Crit Care Med.* 2017;195(5):557-582.

26. Gershon AS, Campitelli MA, Croxford R, et al. Combination long-acting beta-agonists and inhaled corticosteroids compared with long-acting beta-agonists alone in older adults with chronic obstructive pulmonary disease. *JAMA.* 2014;312(11):1114-1121.

27. Ding B, Small M. Treatment trends in patients with asthma-COPD overlap syndrome in a COPD cohort: findings from a real-world survey. *Int J Chron Obstruct Pulmon Dis.* 2017;12:1753-1763.

28. Lee SY, Park HY, Kim EK, et al. Combination therapy of inhaled steroids and long-acting beta2-agonists in asthma-COPD overlap syndrome. *Int J Chron Obstruct Pulmon Dis.* 2016;11:2797-2803.

29. Yi-Fong Su V, Yang KY, Yang YH, et al. Use of ICS/LABA Combinations or LAMA is Associated with a Lower Risk of Acute Exacerbation in Patients with Coexistent COPD and Asthma. *J Allergy Clin Immunol Pract.* 2018.

30. D'Urzo A, Donohue JF, Kardos P, Miravitlles M, Price D. A re-evaluation of the role of inhaled corticosteroids in the management of patients with chronic obstructive pulmonary disease. *Expert Opin Pharmacother.* 2015;16(12):1845-1860.

31. Le Rouzic O, Roche N, Cortot AB, et al. Defining the "Frequent Exacerbator" Phenotype in COPD: A Hypothesis-Free Approach. *Chest.* 2018;153(5):1106-1115.

32. Vogelmeier CF, Bateman ED, Pallante J, et al. Efficacy and safety of once-daily QVA149 compared with twice-daily salmeterol-fluticasone in patients with chronic obstructive pulmonary disease (ILLUMINATE): a randomised, double-blind, parallel group study. *Lancet Respir Med.* 2013;1(1):51-60.

33. Beeh KM, Derom E, Echave-Sustaeta J, et al. The lung function profile of once-daily tiotropium and olodaterol via Respimat((R)) is superior to that of twice-daily salmeterol and fluticasone propionate via Accuhaler((R)) (ENERGITO((R)) study). *Int J Chron Obstruct Pulmon Dis.* 2016;11:193-205.

34. Busch R, Han MK, Bowler RP, et al. Risk factors for COPD exacerbations in inhaled medication users: the COPDGene study biannual longitudinal follow-up prospective cohort. *BMC Pulm Med.* 2016;16:28.

35. Santus P, Buccellati C, Centanni S, et al. Bronchodilators modulate inflammation in chronic obstructive pulmonary disease subjects. *Pharmacol Res.* 2012;66(4):343-348.

36. Bafadhel M, McKenna S, Terry S, et al. Acute exacerbations of chronic obstructive pulmonary disease: identification of biologic clusters and their biomarkers. *Am J Respir Crit Care Med.* 2011;184(6):662-671.

37. Hargreave FE, Dolovich J, Pizzichini E, Pizzichini M. Airway eosinophilia in chronic bronchitis during exacerbations. *Am J Respir Crit Care Med.* 1996;153(5):1726-1727.

38. Saetta M, Di Stefano A, Maestrelli P, et al. Airway eosinophilia in chronic bronchitis during exacerbations. *Am J Respir Crit Care Med.* 1994;150(6 Pt 1):1646-1652.

39. Siva R, Green RH, Brightling CE, et al. Eosinophilic airway inflammation and exacerbations of COPD: a randomised controlled trial. *Eur Respir J.* 2007;29(5):906-913.

40. Brightling CE, Monteiro W, Ward R, et al. Sputum eosinophilia and short-term response to prednisolone in chronic obstructive pulmonary disease: a randomised controlled trial. *Lancet.* 2000;356(9240):1480-1485.

41. Pizzichini E, Pizzichini MM, Gibson P, et al. Sputum eosinophilia predicts benefit from prednisone in smokers with chronic obstructive bronchitis. *Am J Respir Crit Care Med.* 1998;158(5 Pt 1):1511-1517.

42. Bafadhel M, Davies L, Calverley PM, Aaron SD, Brightling CE, Pavord ID. Blood eosinophil guided prednisolone therapy for exacerbations of COPD: a further analysis. *Eur Respir J.* 2014;44(3):789-791.

43. Bafadhel M, McKenna S, Terry S, et al. Blood eosinophils to direct corticosteroid treatment of exacerbations of chronic obstructive pulmonary disease: a randomized placebo-controlled trial. *Am J Respir Crit Care Med.* 2012;186(1):48-55.

44. Dransfield MT, Bourbeau J, Jones PW, et al. Once-daily inhaled fluticasone furoate and vilanterol versus vilanterol only for prevention of exacerbations of COPD: two replicate double-blind, parallel-group, randomised controlled trials. *Lancet Respir Med.* 2013;1(3):210-223.

45. Pascoe S, Locantore N, Dransfield MT, Barnes NC, Pavord ID. Blood eosinophil counts, exacerbations, and response to the addition of inhaled fluticasone furoate to vilanterol in patients with chronic obstructive pulmonary disease: a secondary analysis of data from two parallel randomised controlled trials. *Lancet Respir Med.* 2015;3(6):435-442.

46. Pavord ID, Lettis S, Locantore N, et al. Blood eosinophils and inhaled corticosteroid/long-acting beta-2 agonist efficacy in COPD. *Thorax.* 2016;71(2):118-125.

47. Siddiqui SH, Guasconi A, Vestbo J, et al. Blood Eosinophils: A Biomarker of Response to Extrafine Beclomethasone/Formoterol in Chronic Obstructive Pulmonary Disease. *Am J Respir Crit Care Med.* 2015;192(4):523-525.

48. Vedel-Krogh S, Nielsen SF, Lange P, Vestbo J, Nordestgaard BG. Blood Eosinophils and Exacerbations in Chronic Obstructive Pulmonary Disease. The Copenhagen General Population Study. *Am J Respir Crit Care Med.* 2016;193(9):965-974.

49. Cheng SL, Lin CH. Effectiveness using higher inhaled corticosteroid dosage in patients with COPD by different blood eosinophilic counts. *Int J Chron Obstruct Pulmon Dis.* 2016;11:2341-2348.

50. Barnes NC, Sharma R, Lettis S, Calverley PM. Blood eosinophils as a marker of response to inhaled corticosteroids in COPD. *Eur Respir J.* 2016;47(5):1374-1382.

51. Kostikas K, Brindicci C, Patalano F. Blood eosinophils as biomarkers to drive treatment choices in asthma and COPD. *Curr Drug Targets.* 2018.

52. Cazzola M, Rogliani P, Calzetta L, Matera MG. Triple therapy versus single and dual long-acting bronchodilator therapy in COPD: a systematic review and meta-analysis. *Eur Respir J.* 2018;52(6).

53. Contoli M, Pauletti A, Rossi MR, et al. Long-term effects of inhaled corticosteroids on sputum bacterial and viral loads in COPD. *Eur Respir J.* 2017;50(4).

54. Kolsum U, Donaldson GC, Singh R, et al. Blood and sputum eosinophils in COPD; relationship with bacterial load. *Respir Res.* 2017;18(1):88.

55. Kaplan AG. Applying the wisdom of stepping down inhaled corticosteroids in patients with COPD: a proposed algorithm for clinical practice. *Int J Chron Obstruct Pulmon Dis.* 2015;10:2535-2548.

56. Nannini LJ, Lasserson TJ, Poole P. Combined corticosteroid and long-acting beta(2)-agonist in one inhaler versus long-acting beta(2)-agonists for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev.* 2012(9):CD006829.

57. Calzetta L, Matera MG, Braido F, et al. Withdrawal of inhaled corticosteroids in COPD: A meta-analysis. *Pulm Pharmacol Ther.* 2017;45:148-158.

58. Rossi A, van der Molen T, del Olmo R, et al. INSTEAD: a randomised switch trial of indacaterol versus salmeterol/fluticasone in moderate COPD. *Eur Respir J.* 2014;44(6):1548-1556.

59. Kunz LI, Ten Hacken NH, Lapperre TS, et al. Airway inflammation in COPD after long-term withdrawal of inhaled corticosteroids. *Eur Respir J.* 2017;49(1).

60. Rossi A, Guerriero M, Corrado A, Group OAS. Withdrawal of inhaled corticosteroids can be safe in COPD patients at low risk of exacerbation: a real-life study on the appropriateness of treatment in moderate COPD patients (OPTIMO). *Respir Res.* 2014;15:77.

61. Vogelmeier C, Worth H, Buhl R, et al. "Real-life" inhaled corticosteroid withdrawal in COPD: a subgroup analysis of DACCORD. *Int J Chron Obstruct Pulmon Dis.* 2017;12:487-494.

62. Watz H, Tetzlaff K, Wouters EF, et al. Blood eosinophil count and exacerbations in severe chronic obstructive pulmonary disease after withdrawal of inhaled

corticosteroids: a post-hoc analysis of the WISDOM trial. *Lancet Respir Med.* 2016;4(5):390-398.

63. Vogelmeier C, Paggiaro PL, Dorca J, et al. Efficacy and safety of aclidinium/formoterol versus salmeterol/fluticasone: a phase 3 COPD study. *Eur Respir J.* 2016;48(4):1030-1039.

64. Wedzicha JA, Banerji D, Chapman KR, et al. Indacaterol-Glycopyrronium versus Salmeterol-Fluticasone for COPD. *N Engl J Med.* 2016;374(23):2222-2234.

65. Papi A, Kostikas K, Wedzicha JA, et al. Dual Bronchodilation Response by Exacerbation History and Eosinophilia in the FLAME Study. *Am J Respir Crit Care Med.* 2018;197(9):1223-1226.

66. Roche N, Chapman KR, Vogelmeier CF, et al. Blood Eosinophils and Response to Maintenance Chronic Obstructive Pulmonary Disease Treatment. Data from the FLAME Trial. *Am J Respir Crit Care Med.* 2017;195(9):1189-1197.

67. Vogelmeier CF, Chapman KR, Miravitlles M, et al. Exacerbation heterogeneity in COPD: subgroup analyses from the FLAME study. *Int J Chron Obstruct Pulmon Dis.* 2018;13:1125-1134.

68. Calverley PMA, Tetzlaff K, Vogelmeier C, et al. Eosinophilia, Frequent Exacerbations, and Steroid Response in Chronic Obstructive Pulmonary Disease. *Am J Respir Crit Care Med.* 2017;196(9):1219-1221.

69. Papi A, Kostikas K, Wedzicha JA, et al. Dual Bronchodilation Response by Exacerbation History and Eosinophilia in the FLAME Study. *Am J Respir Crit Care Med.* 2017.

70. Alcazar Navarrete B, Casanova C, Miravitlles M, et al. "Correct use of inhaled corticosteroids in chronic obstructive pulmonary disease": a consensus document. *Arch Bronconeumol.* 2015;51(4):193-198.

71. Harlander M, Barrecheguren M, Turel M, Miravitlles M. Should Patients Switched from D to B in the GOLD 2017 Classification be Discontinued from Inhaled Corticosteroids? *COPD.* 2017;14(5):465-468.

72. Miravitlles M, Cosio BG, Arnedillo A, et al. A proposal for the withdrawal of inhaled corticosteroids in the clinical practice of chronic obstructive pulmonary disease. *Respir Res.* 2017;18(1):198.

73. Cabrera C, Casanova C, Martin Y, et al. Agreement between a simple dyspnea-guided treatment algorithm for stable COPD and the GOLD guidelines: a pilot study. *Int J Chron Obstruct Pulmon Dis.* 2016;11:1217-1222.

74. IPCRG. Evaluation of appropriateness of inhaled corticosteroid (ICS) therapy in COPD and guidance on ICS withdrawal. Available at: https://www.theipcrg.org/display/HOME/.

Figure legends

Figure 1. GOLD 2019 algorithms for initial pharmacological treatment of COPD. [a] Consider if highly symptomatic (e.g. CAT>20). [b] Consider if eosinophils > 300 cells/μL. Note: The figure was adapted from the Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2019 Report.[3]

Figure 2. Decisional tool to guide the most appropriate management of COPD.