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Task force report

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Withdrawal of Inhaled Corticosteroids in Chronic Obstructive Pulmonary Disease: A European Respiratory Society Guideline

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ABSTRACT

Inhaled corticosteroids (ICS) combined with bronchodilators can reduce the frequency of exacerbations in some patients with chronic obstructive pulmonary disease (COPD). There is evidence, however, that ICS are frequently used in patients where their benefit has not been established. Therefore, there is a need for a personalized approach to the use of ICS in COPD and to consider withdrawal of ICS in patients without a clear indication. This document reports European Respiratory Society recommendations regarding ICS withdrawal in patients with COPD.

Comprehensive evidence synthesis was performed to summarize all available evidence relevant to the question. The evidence was appraised using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach and the results were summarized in evidence profiles. The evidence synthesis was discussed and recommendation formulated by a committee with expertise in COPD and guideline methodology.

After considering the balance of desirable and undesirable consequences, quality of evidence, feasibility, and acceptability of interventions, the guideline panel made: a) conditional recommendation for the withdrawal of ICS in patients with COPD without a history of frequent exacerbations; b) strong recommendation not to withdraw ICS in patients with blood eosinophil counts $\geqslant$300 eosinophils·μL−1; c) strong recommendation to treat with one or two long-acting bronchodilators if ICS are withdrawn.

Conditional recommendations indicate that there was uncertainty about the balance of desirable and undesirable consequences of the intervention, and that well-informed patients may make different choices regarding whether to have or not have the specific intervention.

KEYWORDS: COPD; Inhaled corticosteroids; Withdrawal; Exacerbations; Treatment; Guideline.

INTRODUCTION

The use of Inhaled corticosteroids (ICS) combined with long-acting bronchodilators (LABD) is recommended for prevention of exacerbations in patients with moderate to very severe chronic obstructive pulmonary disease (COPD).(1) However, several studies have shown an extensive use of ICS in patients in which they may not be indicated.(2–5) This inappropriate use of ICS may be associated with an increased risk of side effects, in particular in the COPD population, which usually consists of elderly subjects with several comorbidities and high prevalence of frailty.(6–8) These side effects include an increased risk of pneumonia, mycobacterial disease, increased incidence and poor control of diabetes, osteoporosis and bone fractures, dysphonia and oropharyngeal candidiasis, among others.(9–12)

Results of recent clinical trials and observational studies indicate that not all patients with COPD benefit from the use of ICS. In particular, those patients with recurrent exacerbations and higher concentrations of sputum or blood eosinophils demonstrated a better response to ICS, while patients with low blood eosinophil concentrations showed no response to ICS and may be at a higher risk of complications.(13–18)

The lack of response to ICS in some COPD patients, the extensive use of ICS in patients in which they are not indicated and the possibility of development of side effects with the long term use of these drugs have generated interest in the investigation of the possible consequences and benefits of ICS withdrawal. Initial studies of ICS withdrawal in COPD were small and the alternative treatment was either placebo or short-acting bronchodilators (SABD)(19–24); in contrast, more recent studies included large populations of patients with withdrawal to either one or two LABDs .(25,26)

The interest in ICS withdrawal in COPD is reflected in the publication of two meta-analyses(27,28) and several position papers that describe algorithms for the identification of the right patients for discontinuation(5,29–34); moreover, ICS withdrawal has recently been recognised as a potential therapeutic option in the Global Initiative for Chronic Obstructive Lung Disease (GOLD) strategy (www.goldcopd.org).(1).

The purpose of this taskforce was to develop a recommendation that answers the following question: should ICS be withdrawn in patients with COPD? This guideline employed a systematic review of the literature followed by the application of the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach(35).

METHODS

Group composition

This document has been developed following the requirements for guidelines of the European Respiratory Society (ERS)(36). The guideline panel co-chairs (JDC, MM) were selected by the ERS. They led all aspects of project management and selected the guideline panel, which included 11 clinicians and researchers with experience in COPD, an ERS methodologist and a patient representative. A methodology group consisting of two panel members (IFL and JDC) under the supervision of the ERS methodologist (DR) identified and collected the evidence, performed the evidence syntheses, constructed the evidence profiles, and ensured that all the methodological requirements were met. The co-chairs and panelists discussed the evidence and formulated the recommendations. The

guideline was developed using the short guideline format with guideline development completed within 12 months and addressing a single PICO (patient, intervention, comparator, outcomes) question that is considered to be of special clinical interest.

Formulation of question

Guideline panel members agreed on the formulation of the PICO question(37) as follows.

P: Patients with Chronic Obstructive Pulmonary Disease

I: Withdrawal of inhaled corticosteroids with continuation of long acting bronchodilators

C: Continuation of inhaled corticosteroids

O: Exacerbation frequency, respiratory hospitalisations, quality of life measures, adverse effects and pneumonia. Health care resource utilisation, all–cause hospitalisation, FEV_1, use of reliever medication, dyspnoea, exercise capacity and all-cause mortality.

The guideline panel pre-specified that within the population they would examine subgroups based on baseline forced expiratory volume in 1 second (FEV_1), blood eosinophil count and history of frequent exacerbations, if such data were available.

Rating the importance of outcomes

After defining the question, the guideline panel identified outcomes that they considered relevant to it. They rated the importance of each outcome using a scale from 1 to 9 (a rating of 1 to 3 was assigned to outcomes of low importance, 4 to 6 to outcomes important, and 7 to 9 to outcomes critically important for decision-making).

Literature searches

The methodology group conducted a systematic review and meta-analysis of studies according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) recommendations.(38) At the first guideline panel meeting the inclusion and exclusion criteria were agreed upon. Studies included were randomised controlled trials that compared the continuation of ICS and ICS withdrawal in outpatients with stable COPD. COPD was defined as per the GOLD definition.(1) The panel determined that for inclusion in the meta-analysis the ICS withdrawal groups had to be prescribed an alternative LABD therapy, which is the current standard of care.(1) The follow up period for study inclusion was a minimum of six months based on the majority opinion of the panel that most clinically relevant outcomes could not be evaluated within a shorter study duration.

Full details of the literature search and systematic review are described in the online supplement.

Evidence synthesis

Studies were finally selected for inclusion via consensus decision of three authors (IFL, JDC and MM) after review of the full text and the selection was approved by the full panel. Data collection was performed independently by two authors (IFL and JDC) in a blinded fashion for all outcomes of interest. They collected the data into a predesigned spreadsheet for consistency and the data were checked by two other authors (MM and DR). Exacerbation rates were determined via three measures (exacerbation frequency, time to first exacerbation and number of patients experiencing at least one exacerbation). Severe exacerbations were defined as those requiring hospitalisation. Quality of life was

measured with the St Georges Respiratory Questionnaire (SGRQ). Symptoms were measured via dyspnoea scores and the Transition Dyspnoea Index (TDI).

Study characteristics, types of participants, interventions, the outcomes measured, and results were extracted from each study. If the data were amenable to pooling, effects were estimated via meta-analysis using Review Manager Version 5. For the meta-analyses, the random effects model was utilized unless otherwise specified. Dichotomous outcomes were reported as relative risks and continuous outcomes were reported as mean differences unless otherwise specified. The methodology team appraised the quality of evidence using the GRADE approach(39) and a GRADE approach for deprescribing.(35)

GRADEpro was used to develop evidence profiles that summarized the findings for each outcome and the rationale for the quality of evidence appraisal.(37) Thresholds for clinically important changes (used to judge imprecision) included the following relative risk reductions: mortality 15%, exacerbations 20%, hospitalizations 20%, treatment failure 20%, and adverse events 15%. They also included the following absolute reductions: SGRQ score change of 4 points and a FEV_1 change of 100 mL. The thresholds for clinically important relative risk reductions were based upon the task force's collective clinical experience. The thresholds for clinically important absolute risk reductions were based upon published literature.(40) Details of the statistical analysis are described in the online supplement.

Formulating and grading recommendations

Recommendations were formulated on the basis of the following considerations: the balance of desirable (benefits) and undesirable consequences (burden, adverse effects,

cost) of the intervention, the quality of evidence, patient values and preferences, and feasibility.(41)

A strong recommendation was made for an intervention when the panel was certain that the desirable consequences of the intervention outweighed the undesirable consequences, just as a strong recommendation would have been made against an intervention if the panel was certain that the undesirable consequences of the intervention outweigh the desirable consequences. A strong recommendation indicates that most well-informed patients would choose to have or not to have the intervention.

A conditional recommendation was made for an intervention when the panel was uncertain that the desirable consequences of the intervention outweighed the undesirable consequences, just as a conditional recommendation would have been made against an intervention if the panel was uncertain that the undesirable consequences of the intervention outweighed the desirable consequences. Reasons for uncertainty included low or very low quality of evidence, the desirable and undesirable consequences being finely balanced, or the underlying values and preferences playing an important role. A conditional recommendation indicates that well-informed patients may make different choices regarding whether to have or not to have the intervention. Recommendations were formulated using the GRADE evidence to decision framework.

In one area identified as important by the panel but not suitable for formal ratings of quality of evidence, i.e. the modalities of ICS withdrawal, good practice statements were produced as per GRADE guidance.(42)

Manuscript preparation

The initial draft of the manuscript and the online supplement were prepared by the first authors (JDC and IFL) and edited by the chairs and methodologist. Both the manuscript and the online supplement were reviewed, edited, and approved by all panel members prior to submission.

RESULTS

Should inhaled corticosteroids be withdrawn in patients with COPD?

Patients treated with inhaled corticosteroids should be evaluated by recording the frequency of exacerbations and hospitalisations along with measurement of the blood eosinophil count to aid decision making with the following recommendations.

Recommendations:

1) For patients with COPD without a history of frequent exacerbations consider ICS withdrawal (conditional recommendation, moderate quality of evidence)

2) We recommend not to withdraw ICS in patients who have a blood eosinophil count ⩾300 eosinophils·μL−1, with or without a history of frequent exacerbations (strong recommendation, moderate quality of evidence).

3) If ICS are withdrawn, patients should be treated with one or two LABDs (strong recommendation, moderate quality of evidence).

For patients with COPD and a history of frequent exacerbations but <300 eosinophils·μL−1, no recommendation can be formulated due to a lack of evidence. Note that patients without a history of frequent exacerbations are those with no more than one moderate exacerbation in the previous year.

Our literature search found that three studies stopped ICS abruptly while one study withdrew gradually. The absence of meaningful differences in outcomes between these studies suggests that ICS can be abruptly withdrawn in the majority of cases.

Good practice point

Monitoring of exacerbation frequency, symptoms and lung function is recommended following ICS withdrawal. Some patients may deteriorate following any change in treatment, including ICS withdrawal. Therefore ongoing monitoring is appropriate.

Figure 1 summarises these recommendations

Summary of the evidence

Full details of the literature search that informed the guideline development are provided in the online supplement. We identified a total of 1603 papers and once duplicates were removed, the total was 1385. Ultimately four studies met all inclusion and no exclusion criteria and were included in the meta-analysis: COSMIC(21), WISDOM(25), INSTEAD(43) and SUNSET(26). All four trials were funded by the pharmaceutical industry.

The total number of patients in the four trials was 4492. Patients were included in all four studies if they were over the age of 40 years with a history COPD defined as having had a smoking history of at least 10 pack-years and a post-bronchodilator FEV_1 to FVC ratio less than 0.70 (COSMIC used 88% or 89% of predicted according to gender). Patients with moderate to very severe COPD and stable disease status with the absence of

exacerbation during the screening or run-in periods were included. Patients with other respiratory disorders, particularly asthma, or on long-term oxygen therapy were excluded. The majority of patients recruited were not frequent exacerbators with the exception of the patients recruited to the COSMIC study who were required to have had at least two exacerbations in the previous year.(21)

There was variability in the treatment strategies and ICS use prior to recruitment to the studies. The COSMIC trial had a run in period of 12 weeks where patients were treated with salmeterol and fluticasone propionate (SFC) 50/500 micrograms twice daily. The groups were then assigned to either continuing SFC or switching to salmeterol 50 micrograms twice daily for one year.(20) Patients recruited to the INSTEAD trial were included if they had received treatment with SFC 50/500 micrograms for at least three months prior to screening. After a 14-day run-in period, the participants were randomised to continue the SFC therapy or switch to indacaterol 150 micrograms once daily for 26 weeks.(42) At the time of screening for the WISDOM trial, patients were given triple therapy (SFC 50/500 micrograms twice daily and tiotropium 18 micrograms once daily) for a run-in period of six weeks. They were then randomised to either continue triple therapy or have the fluticasone reduced in a stepwise manner over the first 12 weeks and continued on the assigned therapy until 12 months of follow up.(24) Not all participants in the WISDOM study were receiving ICS therapy prior to the run-in period. The SUNSET trial recruited patients who had been on triple therapy for at least six months prior to screening. Patients were all given SFC 50/500 micrograms twice daily with tiotropium 18 micrograms daily during a four-week run-in period before being randomised to either continue triple therapy or switch to indacaterol/glycopyrronium once daily for 26 weeks.(25)

Meta-analyses were performed on the outcomes rated as critical and the subgroup analysis on baseline eosinophils. There was insufficient data to perform subgroup analyses on FEV_1 and prior exacerbation frequency due to a lack of data. The results are summarised below and a full description is provided in the online supplement. Data for important outcomes were extracted and are presented in the online supplement.

Critical outcomes: benefits and harms

Exacerbation endpoints

The meta-analysis found that ICS withdrawal was not associated with an increased frequency of exacerbations. The effect estimate for frequency of moderate or severe exacerbations was rate ratio (per patient per year) 1.05 (95% CI 0.97 to 1.13, p=0.23, I^2=0%) over 6 or 12 months with no significant difference between ICS withdrawal and continuation. Time to first moderate or severe exacerbations was measured in three studies(25,26,43) with no effect of ICS withdrawal, hazard ratio (HR) 1.04 (95% CI 0.94 to 1.16, p=0.42, I^2=2%). For the number of patients experiencing at least one moderate or severe exacerbation, which was reported in two studies(21,43), there was no significant effect: odds ratio (OR) 0.84 (95% CI 0.63 to 1.14, p=0.26, I^2=0%).

For the endpoint of hospitalization for severe exacerbations we did not perform meta-analysis as there were only data from two studies.(25,43) In the INSTEAD trial ICS withdrawal had an OR of 0.49 (95% CI 0.04 to 5.43, p=0.56) favouring ICS withdrawal; however there were very few patients with severe exacerbations (N=1 ICS withdrawal and N=2 ICS continuation). The WISDOM trial measured time to first severe

exacerbation, which resulted in a HR of 1.20 (95% CI 0.98 to 1.48, p=0.08) for ICS withdrawal.

Number of patients with at least one severe exacerbation was considered a critical outcome, but information about this variable was available in only one study. In addition, this study included stable patients and the number of events were extremely low. Despite grading this outcome as with low quality of evidence, we believe that it does not downgrade the overall quality of evidence of the recommendation.

Quality of Life

The SGRQ was performed in all four studies and the pooled mean difference between the two arms was -0.87 points (95% CI -1.72 to -0.02, p=0.05, I^2=21%) suggesting a very small and clinically insignificant worsening in quality of life.(21,25,26,43)

Adverse effects

There were no statistically significant differences between ICS withdrawal and continuation in the number of patients experiencing adverse events in the pooled analysis of three studies, OR 0.94 (95% CI 0.82 to 1.08, p=0.41, I^2=55%).(25,26,43) Hospitalisations for serious adverse events were similar between the two groups in the WISDOM study, 271/1242 (21.8%) vs 273/1243 (21.9%), ICS withdrawal vs continuation respectively.(25)

Pneumonia

Three studies provided data on pneumonia that were suitable for meta-analysis. The results were not statistically significant, OR 0.89 (95% CI 0.64 to 1.22, p=0.46, I^2=0%).

Absolute numbers of pneumonia events were low with 74/1792 (4.13%) in the ICS withdrawal group and 83/2057 (4.04%) in the ICS continuation group.(25,26,43)

FEV_1

FEV_1 was classified as important but not critical for decision making by the panel. In the COSMIC study, there was a significant reduction in pre-dose FEV_1 after the ICS run-in period with an adjusted difference of 4.1 percentage points favouring ICS continuation. The absolute difference between the two arms of the study after 12 months was 50 mL(95% CI 10 to 100 mL, p=0.022).(21)

In the WISDOM study, the adjusted mean reduction in trough FEV_1 from baseline end of the study at week 52 was an adjusted mean reduction of 43 mL greater in the ICS withdrawal group.(25)

In INSTEAD, the least squares mean difference was -0.009 L (95% CI -0.045 to 0.026 L), which was not statistically significant. It was reported that there were no significant differences between the groups at other time points during the study.(43)

At the end of the SUNSET study (day 182), the difference in least squares mean for trough FEV_1 from baseline was -26 mL (95% CI -53 to 1 mL, p=0.0573). There was a consistently lower mean trough FEV_1 in the ICS withdrawal group compared to the ICS continuation and the results were statistically significant until day 181.(26)

Use of rescue medication

The mean percentage of rescue medication free days in the COSMIC study was 47% (standard error (SE) 2%) in ICS withdrawal group and 53% (SE 2%) in the continuation group (p=0.014).(21) In the INSTEAD trial the percentages of rescue mediation free days were 52.8% vs 54.6% (p=0.505) in the ICS withdrawal and continuation groups respectively.(43) The mean change in puffs per day of rescue medication were -0.44 vs -0.49 respectively, with a difference of 0.05 (95% CI -0.17 to 0.28, p=0.650).(42) In the SUNSET trial the difference in puffs per day between the two arms was 0.177 (95% -0.01 to 0.36) and the difference in rescue medication free days between the two arms was 0.103 (95% CI -3.25 to 3.25).(26)

Dyspnoea

No clinically significant differences were observed in measures of dyspnoea in the reported studies. Results are summarised in the online supplement.

All-cause mortality

Overall, all-cause mortality was low in the three studies in which it was reported and there were no significant differences between the two groups (online supplement).

Other endpoints

No data was presented for types of exacerbations, healthcare resource utilisation, all-cause hospitalizations or exercise capacity.

Subgroup Analyses

Of the pre-specified subgroups to examine, data were only available for blood eosinophil counts in more than one study (WISDOM and SUNSET).(25,26,44) The most significant

findings were when comparing baseline eosinophils of <300 cells·μL−1 to ≥300 cells·μL−1 on moderate or severe exacerbation rates between the ICS withdrawal and continuation groups.

In patients with eosinophil counts <300 cells·μL−1 there was no effect of ICS withdrawal on exacerbation rate, rate ratio 1.03 (95% CI 0.90 to 1.18, p=0.71, I^2=0%), but there was a significant increase in exacerbations in patients with eosinophil counts ≥300 cells·μL−1, RR 1.63 (95% CI 1.24 to 2.14, p=0.0005, I^2=0%). The test for subgroup interaction was significant (p=0.02). Similar results were found when comparing baseline eosinophils of <2% vs ≥2%, RR 1.00 (95% CI 0.82 to 1.21, p=1.00, I^2=0%) vs RR 1.22 (95% CI 1.04 to 1.43, p=0.01, I^2=0%) respectively. There were no significant differences between the two groups on moderate or severe exacerbation rates when comparing baseline eosinophils of <150 cells·μL−1or 150-299 cells·μL−1 (figure 2).(25,43)

Conclusions and research needs

Inhaled corticosteroid withdrawal does not increase exacerbation frequency or result in clinically important changes in symptoms or lung function. The evidence is limited due to the small number of studies that met the inclusion criteria, but supports the safety of ICS withdrawal in appropriate patients. This is supported by prior meta-analyses which used broader inclusion criteria including studies that withdrew patients to placebo or SABD or included studies of shorter duration.(27,28)

Subgroup data for baseline eosinophil counts suggest an important effect on exacerbations, which is reflected in the recommendations. There were insufficient data to

perform meaningful subgroup analyses on the other pre-specified subgroups of interest, particularly past history of exacerbations and baseline FEV_1.

The studies used a single eosinophil count at baseline and the evidence suggests that this is sufficient to guide withdrawal.(44) Pragmatically the panel acknowledges that multiple historic eosinophil counts may be available and if several of them, measured during clinical stability, are below 300 cells·μL−1this would increase confidence in ICS withdrawal.

Patients in the majority of the trials were infrequent exacerbators (0-1 in the previous 12 months) apart from the COSMIC study and both the evidence for ICS use in patients with frequent exacerbations and the somewhat worse outcomes for patients in the COSMIC study support only attempting ICS withdrawal in patients with less than two exacerbations per year.(21)

Our analysis was not designed to answer whether patients withdrawing from ICS should receive a single or dual LABD treatment. Most studies suggest superiority of dual LABD therapies for endpoints of lung function and symptoms and so the practice of most panel members would be to use dual LABD therapy.(45–48)

Future studies should therefore prospectively test algorithms for ICS discontinuation based on blood eosinophils as well as establish whether ICS withdrawal is feasible or desirable in patients with 2 or more exacerbations per year. It has been demonstrated that ICS primarily reduce exacerbations requiring corticosteroids, but may increase antibiotic requiring exacerbations, (49) and these endotypes are relatively stable over time.(50) Studies aimed to establish whether exacerbation endotype or other patient characteristics

such as lung function may predict response to withdrawal are also needed. Future trials may therefore establish whether requirement for corticosteroids at exacerbation, the presence of eosinophilic exacerbations or the lung microbiome may predict response to ICS withdrawal.(50,51)

Values and preferences

There is likely to be uncertainty and variability in interpretation of magnitude of effects. The guideline panel experience is that some clinicians and some patients interpret small changes in exacerbations, SGRQ or FEV_1 as important while others may not regard them as clinically significant.(40) Likewise patient feedback was that the majority of patients would give high value to exacerbations and symptoms with low value given the lung function changes in the absence of any impact on symptoms. This is consistent with the systematic review performed by Zhang et al (52), which rated exacerbations and hospital admissions due to exacerbations as the most important endpoints for patients. The patient's personal experience was that most patients would accept ICS withdrawal where this was appropriate. Patients consider it important to avoid withdrawal if this can result in harm and so the availability of a biomarker (blood eosinophils) that could identify patients most likely to benefit from withdrawal was regarded as highly valuable.

DISCUSSION

Inhaled corticosteroids are widely used in the treatment of patients with COPD.(53,54) The availability of combined LABDs and increasing recognition of the potential adverse effects of ICS treatment has led to a gradual re-evaluation of their role.(1,55) The most recent GOLD document separates initial and ongoing pharmacotherapy for COPD and it is notable that LABD therapy, rather than ICS containing therapies are recommended as

initial therapy for all but a small subgroup of patients.(1) Despite this, there is evidence that up to 70% of patients with COPD without a history of frequent exacerbations receive ICS as their initial therapy, even after co-existing asthma is excluded.(3,56,57) This suggests widespread overuse or inappropriate use of ICS. Notably, lung function and symptoms may be improved with dual LABD compared to a combination of ICS/LABA, while there are conflicting data on which is superior for preventing exacerbations.(56,58–61)

It is therefore important to consider whether ICS withdrawal may be appropriate for some individuals who do not require ICS. Barriers to ICS withdrawal are concerns that patients may experience an increase in exacerbations, an increase in symptoms, a worsening of lung function or that patients may experience adrenal insufficiency due to abrupt withdrawal of corticosteroids.

The existing evidence suggests that these concerns are largely unfounded when ICS withdrawal is performed in patients without blood eosinophil counts greater than 300 cells·μL−1 and without a history of frequent exacerbations. No significant impact of ICS withdrawal on exacerbation frequency was observed, and the differences in quality of life and lung function over 6-12 months were small and not likely to be clinically relevant. Notably, all studies except WISDOM abruptly withdrew ICS with no reports of sudden deteriorations or adrenal insufficiency, suggesting no requirement for gradual withdrawal.

In contrast in patients with elevated eosinophil counts (>300 cells·μL−1) there was a large increase in exacerbation frequency that all clinicians would agree is unacceptable. For

this reason, despite being based on only two studies, we make a strong recommendation to maintain ICS treatment in patients with evidence of eosinophilic inflammation. This recommendation is supported by extensive evidence showing that blood eosinophil counts reflect, to some degree, the extent of eosinophilic airway inflammation and predict response to ICS.(14,23,61–64) Based on this data, GOLD recently introduced blood eosinophil counts into the decision making process for ICS initiation. For initial therapy GOLD recommends the same threshold of 300 eosinophils·μL−1 to initiate ICS in patients in group D (more symptomatic, with frequent exacerbations); however in follow-up GOLD recommends to consider the addition of an ICS to LABD in patients with eosinophil counts >100 cells·μL−1 if they had two or more moderate exacerbations or one severe, and to avoid ICS in patients with levels below this.(1) This is based on analysis of recent trials which demonstrate no benefit of ICS/LABA/LAMA vs LABA/LAMA in patients with eosinophil counts <100 cells·μL−1 and evidence of benefit above this level.(14,61) New initiation of ICS in patients with a history of frequent exacerbations is clearly different to withdrawal of ICS in patients without a history of exacerbations. This was supported by our finding of no increase in exacerbations following withdrawal in patients with eosinophil counts between 150 and 300 cells·μL−1. Notably although prior studies powered to investigate an effect of ICS on mortality failed to demonstrate statistically significant differences between ICS containing regimens and long acting beta-agonists alone(65,66), recent studies have suggested a potential mortality benefit over 12 months with ICS/LABA/LAMA therapy compared to dual bronchodilator therapy.(61,67) The potential that ICS withdrawal could have a negative impact on mortality was considered by the panel, but was not considered relevant because the impact of ICS on mortality remains to be clearly established; this effect has only been reported in patients with a history of frequent exacerbations which is a different population to those

being recommended for ICS withdrawal; no trend towards increase mortality was observed in the studies of ICS withdrawal.

We did not observe clear benefits of ICS withdrawal, but this is not surprising as the primary benefits, such as a reduced risk of pneumonia, fractures or other adverse effects may require more than 12 months of follow-up. Notably, observational studies do suggest significant reductions in adverse events such as pneumonia following ICS withdrawal.(68)

Our recommendations do not apply to patients with asthma and we do not address in this guideline how to differentiate asthma and COPD.(69) The trials included in our meta-analysis all excluded patients with asthma and so our guideline algorithm begins with a clear instruction to exclude asthma. We identified various algorithms or position documents which also suggest taking into account prior history of pneumonia, mycobacterial disease, bronchiectasis and other co-morbidities when considering the appropriateness of ICS.(68,70–75) There is insufficient evidence to demonstrate if any of these factors modify the outcome after ICS withdrawal, but clinicians may take such factors into account when deciding how to apply our recommendations. Other factors which may be taken into account include the history of prior response to ICS and exacerbation history prior to ICS. The studies did not consider patients exacerbation frequency prior to commencing ICS therapy. The conditional recommendation in this guideline means that clinicians should make a judgement taking into account the views of patients and their individual benefit: risk. A patient with an eosinophil count <150 cells·μL−1 and no history of exacerbations with no objective benefit from ICS would be a clear candidate for ICS withdrawal. A patient who had >2 exacerbations per year prior

to starting ICS therapy and an eosinophil count between 150-300 cells·μL−1, who has objectively and subjectively benefited from ICS may choose to withdraw ICS or may choose not to withdraw ICS. Guidelines should only be used alongside clinical judgement. Indeed although we make a strong recommendation to avoid ICS withdrawal in patients with elevated eosinophil counts, observational studies suggest that in clinical practice, carefully selected patients with eosinophil counts greater than 300cells·μL−1 do sometimes withdraw from ICS therapy without a significant increase in exacerbations.(76)

In conclusion, we present ERS guidance on the withdrawal of inhaled corticosteroids in COPD. The guideline recommendations and associated considerations are summarised in figure 3 below.

CONFLICTS OF INTEREST

JDC has received speaker fees from Astrazeneca, Boehringer Ingelheim, Glaxosmithkline and Insmed.Consultancy fees for Astrazeneca, Boehringer Ingelheim, Glaxosmithkline, Grifols, Insmed, Zambon. He holds research grants from Astrazeneca, Boehringer Ingelheim, Glaxosmithkline, Gilead Sciences Grifols and Novartis.

NR reports grants and personal fees from Boehringer Ingelheim, Novartis, Pfizer and personal fees from Teva, GSK, AstraZeneca, Chiesi, Mundipharma, Cipla, Sanofi, Sandoz, 3M, Trudell, Zambon.

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DR works as a methodologist for the ERS.

MJM and IFL report no conflicts of interest.

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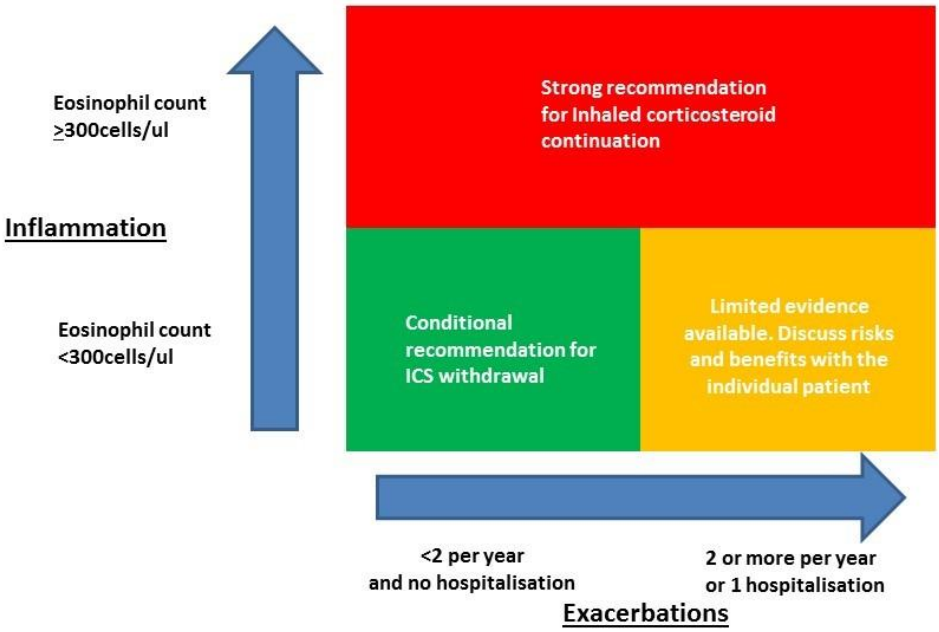
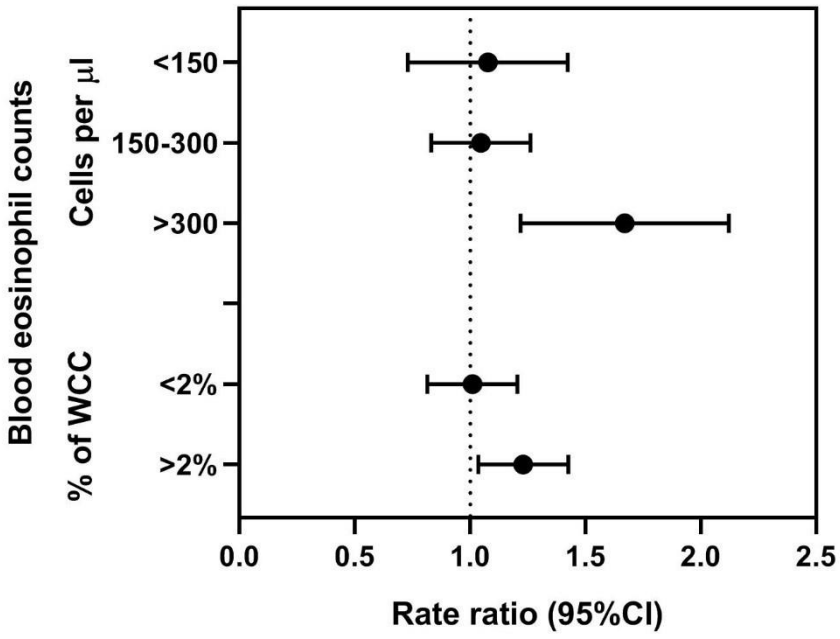
Figure legends

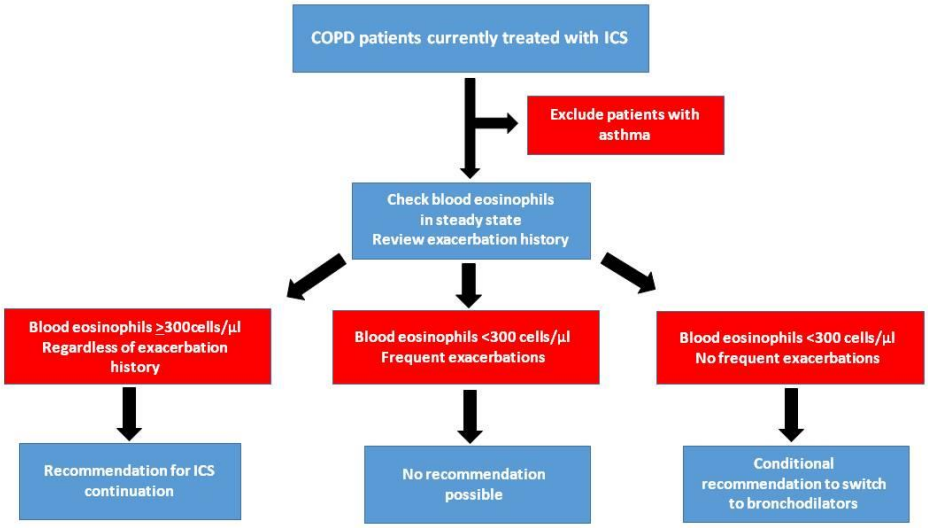
Figure 1. Summary of the guideline recommendations.
Footnote: We recommend taking account of prior exacerbation history and blood eosinophil counts. Patients with high rate of exacerbations and eosinophil counts greater than 300 cells·μL−1 should not be considered for ICS withdrawal. Patients not meeting these criteria may be candidates for ICS withdrawal.

Figure 2. Frequency of moderate and severe exacerbations after ICS withdrawal stratified by baseline blood eosinophil counts.
Footnote: Statistically significant increased exacerbation frequency is observed in patients with blood eosinophil counts greater than 300 cells·μL−1 or ≥2% of total white cell count (WCC).

Figure 3. Summary of ERS guideline on Inhaled Corticosteroid Withdrawal in patients with COPD.
Footnote: Note that systemic corticosteroids suppress blood eosinophil counts and so values taken during or after a recent course of oral corticosteroids should not be used.


Eosinophil count
≥300cells/ul
Inflammation
Eosinophil count
<300cells/ul
Strong recommendation for Inhaled corticosteroid continuation
Conditional recommendation for ICS withdrawal
Limited evidence available. Discuss risks and benefits with the individual patient
<2 per year and no hospitalisation
2 or more per year or 1 hospitalisation
Exacerbations


Blood eosinophil counts
Cells per μl
<150
150-300
>300
% of WCC
<2%
>2%
0.0
0.5
1.0
1.5
2.0
2.5
Rate ratio (95%CI)



- Frequent exacerbations: ≥2 moderate or 1 severe exacerbation/year
- Consider history of exacerbations prior to ICS
- Assess ICS side effects and risk of pneumonia
- Address patient preferences

Online supplement to

Withdrawal of Inhaled Corticosteroids in Chronic Obstructive Pulmonary Disease: A European Respiratory Society Guideline

Methods

Search Strategy

We conducted a systematic review and meta-analysis of studies according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) recommendations to determine if ICS can be withdrawn safely in patients with chronic obstructive pulmonary disease (COPD). The panel agreed upon the inclusion and exclusion criteria. Studies included were randomised controlled trials that compared the continuation of inhaled corticosteroids (ICS) and ICS withdrawal in outpatients with stable COPD. COPD was defined as per the Global Initiative of Chronic Obstructive Pulmonary Disease. The panel determined that for inclusion in the meta-analysis the ICS withdrawal groups had to be prescribed an alternative long-acting bronchodilator therapy, which is the current standard of care. The follow up period for study inclusion was a minimum of six months. Studies were excluded if the ICS withdrawal group was transitioned to placebo or short-acting bronchodilator therapy only.

One author (IFL) searched for papers published from the inception of the database to May 2019 using Pubmed (Medline), CINAHL and EMBASE. No limits were placed on the database searches. Studies searched were not limited by language and the full-text was sourced if necessary via interlibrary loans. Searches were also supplemented by reviewing the reference lists of the publications and review articles. Additional data were sourced from supplementary material and post-hoc analyses.

The search terms used were as follows:
Pubmed
1 (((((("copd") OR "coad") AND ("inhaled corticosteroid" OR "inhaled glucocorticoid") AND withdraw*) AND exacerbation)
2 COPD and (inhaled corticosteroid or inhaled glucocorticoid) and randomised controlled trial
3 (pulmonary disease, chronic obstructive) AND (inhalers) AND (glucocorticoids OR triple therapy OR LAMA OR LABA OR beta agonist OR anticholinergic OR muscarinic antagonist) AND (withdrawal OR de-escalation OR switch OR discontinuation)

CINAHL
1 ((MH "Pulmonary Disease, Chronic Obstructive+")) AND (((MH "Administration, Inhalation") OR "inhaled corticosteroid") OR ("inhaled glucocorticoid") OR "ICS") AND ("withdraw*" OR "cease" OR "cessation" OR "de-escalat*" OR "switch" OR "discontin*" OR "chang*")

EMBASE
1 ((COPD or chronic obstructive pulmonary disease or chronic obstructive lung disease or chronic obstructive airways disease) and (ICS or inhaled corticosteroid or inhaled glucocorticoid) and (LAMA or LABA or triple therapy or dual therapy or bronchodilator or long acting beta agonist or anti-muscarinic or anticholinergic) and (withdraw* or de-escalat* or switch* or chang* or discontinu* or cease or cessation)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

Outcomes

The panel determined the outcomes of interest for the meta-analysis, which were rated as either critical or important. The outcomes that were rated as critical were exacerbation rates, respiratory hospitalisations, quality of life measures, adverse effects and pneumonia. The remainder of the outcomes were rated as important and included type of exacerbations, health care resource utilisation, all–cause hospitalisation, FEV_1, use of reliever medication, dyspnoea, exercise capacity and all-cause mortality. Pre-specified subgroup analyses of interest were

eosinophil levels, prior exacerbation history and baseline FEV_1. We also sought data on history of asthma, dosage of ICS, duration of ICS prior to withdrawal, the period of time over which ICS were withdrawn (abrupt vs stepwise or gradual) and prior type of therapy (triple therapy, ICS/long-acting beta agonist (LABA) or unspecified).

Data analysis
Studies were selected for inclusion via consensus decision of three authors (IFL, JDC and MM) after review of the full text and the selection was approved by the full panel. Data collection was performed independently by two authors (IFL and JDC) in a blinded fashion for all outcomes of interest. We collected the data onto a predesigned spreadsheet for consistency and the data were checked by two other authors (MM and DR). Exacerbation rates were determined via three measures (exacerbation frequency, time to first exacerbation and number of patients experiencing at least one exacerbation). Respiratory hospitalisations were taken from the rates of severe exacerbations since severe exacerbations were defined as those requiring hospitalisation. Quality of life measures used were the St Georges Respiratory Questionnaire (SGRQ) and the Clinical COPD Questionnaire (CCQ). Symptoms were measured via dyspnoea scores and the Transition Dyspnoea Index (TDI).

Statistical analysis
We performed the meta-analysis for all critical outcomes and for subgroups where there were sufficient data using Review Manager (RevMan) [Computer program]. Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

We collected the number of patients who had each outcome and the denominator for categorical outcomes and the sample size and mean or median depending on how the data were presented in the studies for continuous outcomes. We collected the number of patients in each group, effect estimate and confidence intervals for effect estimates. We selected the intention-to-treat datasets when more than one set of results were reported. Significance for p values was set at a threshold of 0.05.

For dichotomous outcomes, data are presented as pooled risk ratios or odds ratios (ORs) and 95% CIs. Continuous variables are presented as mean differences with 95% CI. Effect estimates of time to event data or rate ratios were pooled by the inverse of their variance and are presented as pooled effect estimates (hazard ratios [HRs] or rate ratios) with corresponding 95% CIs. All analyses used random effects meta-analysis using the method of DerSimonian and Laird because of the heterogeneity of study designs. The threshold for significance for p values was 0.05.

The I^2 statistic was used to describe heterogeneity between studies. This represents the percentage of variation across studies due to heterogeneity rather than chance, and was calculated as previously described. Low heterogeneity was less than 30%, moderate heterogeneity was 30-60% and high heterogeneity was greater than 60%.

The subgroup analysis was performed for eosinophil levels at baseline, which was the only pre-specified subgroup with sufficient data. The data were analysed as effect estimates and are presented as rate ratios with 95% confidence intervals.

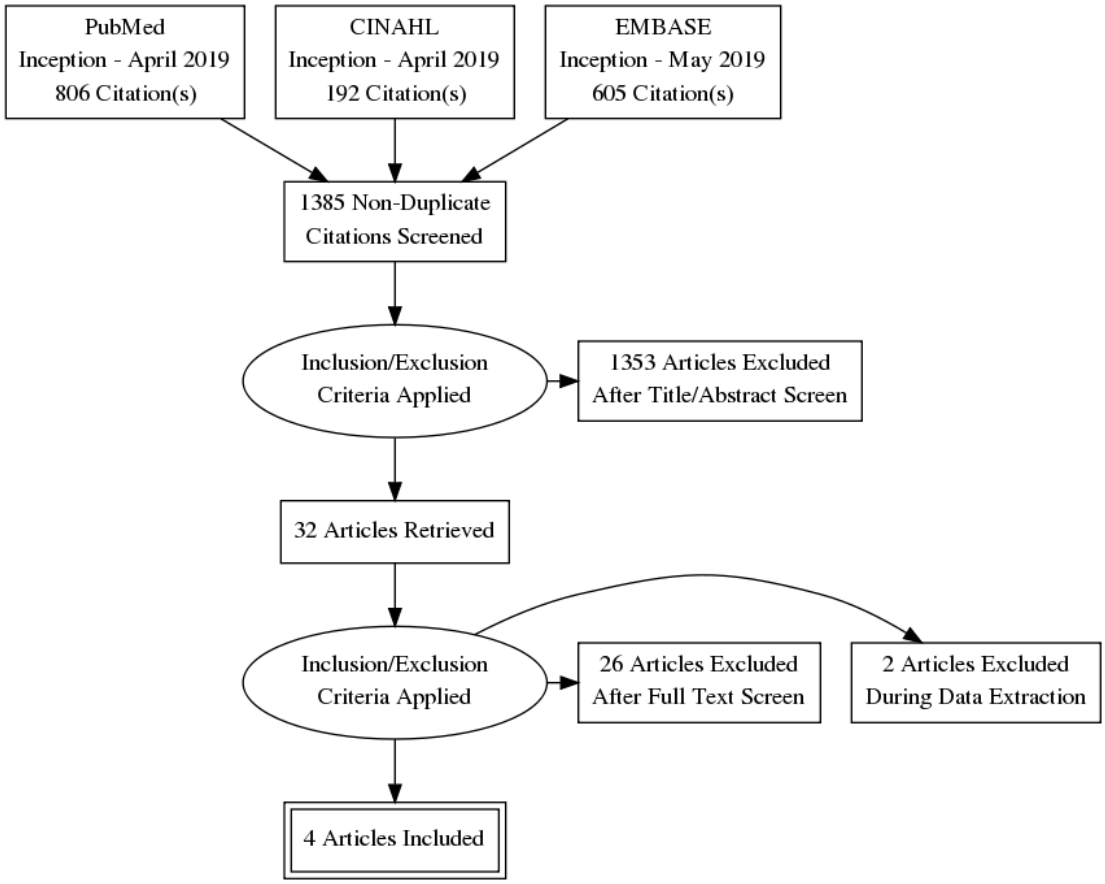
The risk of bias and evidence grading were assessed by four authors (IFL, JDC, MM and DR) using GRADEpro Guideline Development Tool [Software]. McMaster University, 2015 (developed by Evidence Prime, Inc.). Available from gradepro.org.

The Evidence to Decision framework was completed at a meeting attended by the majority of the panel, which included patient representatives.

Results (extended)

Summary of the evidence
The database searches revealed a total of 1603 of papers and once duplicates were removed, the total was 1385. Once the inclusion and exclusion criteria were applied by the authors, four studies were included in the meta-

analysis: COSMIC (Wouters et al, Thorax 2005), WISDOM (Magnussen et al, NEJM 2014), INSTEAD (Rossi et al, ERJ 2014) and SUNSET (Chapman et al, AJRCCM 2018).



The total number of patients in the four trials was 4492. Patients were included in all four studies if they were over the age of 40 years with a history COPD defined as having had a smoking history of at least 10 pack years and a FEV_1 to FVC ratio less than 0.70 (with the exception of the COSMIC study (0.88 or 0.89 predicted according to gender)). Patients with moderate or severe COPD and stable disease status (ie no exacerbations) during the screening or run-in periods were included. Patients with other respiratory disorders or on long-term oxygen therapy were excluded. The majority of patients recruited were not frequent exacerbators (INSTEAD, SUNSET, WISDOM) with the exception of the patients recruited to the COSMIC study who were required to have had at least two exacerbations in the previous year.

There was variability in the treatment strategies and ICS use prior to recruitment to the studies. The COSMIC trial had a run in period of 12 weeks where patients with treated with Salmeterol and fluticasone proprionate (SFC) 50/500 micrograms twice daily. The groups were then assigned to either continuing SFC or switch to salmeterol 50 micrograms twice daily for one year. Patients recruited to the INSTEAD trial were included if they had received treatment with SFC 50/500 micrograms for at least three months prior to screening. After a 14-day run-in period, the participants were randomised to continue the SFC therapy or switch to indacaterol 150 micrograms once daily for 26 weeks. At the time of screening for the WISDOM trial patients were in dual bronchodilator therapy and were given triple therapy (SFC 50/500 micrograms twice daily and tiotropium 18 micrograms once daily) for a run-in period of six weeks. They were then randomised to either continue triple therapy or have the fluticasone dose weaned in a stepwise manner over the first 12 weeks and continued on the assigned therapy until 12 months of follow up. The SUNSET trial recruited patients who had been on triple therapy for at least six months prior to screening. Patients were all given SFC 50/500 micrograms twice daily with tiotropium 18 micrograms daily during a four-week run-in period before being randomised to either continue triple therapy or switch to indacaterol/glycopyrronium 110/50 micgrograms once daily for 26 weeks. Patients were given placebo inhalers to conceal the treatment protocol to which they had been assigned.

Meta-analyses were performed on the outcomes rated as critical and the subgroup analysis on baseline eosinophils. Other results are presented descriptively.

Critical outcomes

Exacerbation endpoints

Exacerbation endpoints reported in the included studies were exacerbation frequency, time to first exacerbation and number of individuals with at least one exacerbation. All studies reported moderate and severe exacerbations together as a single endpoint. However, one study (INSTEAD) reported mild, moderate and severe together and did not specify moderate and severe separately for the frequency endpoint. As the mild event rate was low in this study the data were pooled with a sensitivity analysis performed excluding this study. Moderate exacerbations were defined as requiring therapy such as antibiotics and/or systemic corticosteroids and severe exacerbations were defined as requiring hospitalisation.

The meta-analysis found that inhaled corticosteroid withdrawal was not associated with an increased frequency of exacerbations. The effect estimate for the endpoint of frequency of moderate or severe exacerbations was rate ratio (RR) 1.05 (95% CI 0.97 to 1.13, p=0.23, I^2=0%) across all four studies at the end of treatment (6 or 12 months) with no significant difference between ICS withdrawal and continuation. Time to first moderate or severe exacerbations was measured in three studies (WISDOM/INSTEAD/SUNSET) with no clear effect of inhaled corticosteroid withdrawal, hazard ratio (HR) 1.04 (95% CI 0.94 to 1.16, p=0.42, I^2=2%). For the effect estimate of the number of patients experiencing at least one moderate or severe exacerbation, which was reported in two studies (COSMIC/INSTEAD), the effect was odds ratio (OR) 0.84 (95% CI 0.63 to 1.14, p=0.26, I^2=0%).

The annual moderate or severe exacerbation rates were 1.6 per patient-year in the ICS withdrawal group and 1.3 per patient-year in the ICS continuation group in the COSMIC study. In the WISDOM study, the adjusted event rate was 0.95 per patient-year in the ICS withdrawal group and 0.91 per patient-year in the ICS continuation group. The rate of all exacerbations per year was 0.57 vs 0.67 in the ICS withdrawal and continuation groups respectively in the INSTEAD trial. In the SUNSET trial, the annual rate of moderate or severe exacerbations was 0.52 vs 0.48 in the ICS withdrawal and continuation groups respectively.

Respiratory Hospitalisations

Respiratory hospitalization and severe exacerbations were used interchangeably in the studies and therefore in our meta-analysis. In the INSTEAD trial for the endpoints of the number of patients experiencing at least one severe exacerbation, ICS withdrawal resulted in an OR of 0.49 (95% CI 0.04 to 5.43, p=0.56) favouring ICS withdrawal; however there were very few patients with severe exacerbations (N=1 ICS withdrawal and N=2 ICS continuation). The WISDOM trial measured time to first severe exacerbation, which resulted in a HR of 1.20 (95% CI 0.98 to 1.48) for ICS withdrawal. As there are only two studies, we did not provide a pooled effect estimate.

Quality of Life

The St George's Respiratory Questionnaire (SGRQ) was performed in all four studies and the pooled mean difference between the two arms was -0.87 (95% CI -1.72 to -0.02, p=0.05, I^2=21%). The COPD Assessment Test (CAT) was not included in any of the studies. The Clinical COPD Questionnaire (CCQ) was used in the COSMIC study and there was a difference of 0.13 (standard error (SE) 0.06), p=0.041 between the two groups after 12 months with higher scores indicating worse symptoms in the ICS withdrawal group at all time points during the study, except at the 12 month point.

Adverse effects

The COSMIC study was not included in the meta-analysis as the data were presented as the total number of adverse events rather than number of patients with adverse events. The number of adverse events was similar in both arms in this study: total adverse events 516 vs 529 and treatment related adverse events 25 vs 26, ICS withdrawal vs continuation respectively. There were no statistically significant differences between ICS withdrawal and continuation in the number of patients experiencing adverse events in the pooled analysis of the other three studies, OR 0.94 (95% CI 0.82 to 1.08, p=0.41, I^2=55%).

Pneumonia

The rates of pneumonia were not available in the COSMIC study. The other three studies were included in the meta-analysis and the results favoured ICS withdrawal, but were not statistically significant, OR 0.89 (95% CI 0.64 to 1.22,

p=0.46, I^2=0%). Absolute numbers of pneumonia events were low with 74/1792 (4.13%) in the ICS withdrawal group and 83/2057 (4.04%) in the ICS continuation group.

Important Outcomes

Types of exacerbations
There were no other results or data presented for specific types of exacerbations other than what has already been described.

Health care resource utilisation
No data were provided on health care resource utilisation in these studies.

All-cause hospitalisations
There were no results for all-cause hospitalisations. Hospitalisations for serious adverse events were similar between the two groups in the WISDOM study, 271/1242 (21.82%) vs 273/1243 (21.96%), ICS withdrawal vs continuation respectively.

FEV_1
In the COSMIC study, there was a significant reduction in pre-dose FEV_1 after the ICS run-in period with an adjusted difference of 4.1 percentage points favouring ICS continuation. The difference between the two arms of the study after 12 months was 50 mL (95% CI 10 to 100 mL, p=0.022).

At the end of the ICS withdrawal period at week 18 in the WISDOM study, the adjusted mean reduction in trough FEV_1 from baseline was 38 mL greater in the ICS withdrawal group and remained similar at the end of the study at week 52 with an adjusted mean reduction of 43 mL greater in the ICS withdrawal group.

In INSTEAD, the least squares mean values for trough FEV_1 at week 12 were 1.584 (SE 0.0294) L for ICS withdrawal and 1.593 (SE 0.0300) L for ICS continuation with a difference of -0.009 L (95% CI -0.045 to 0.026 L), which was not statistically significant. It was reported that there were no significant differences between the groups at other time points during the study.

At the end of the SUNSET study (day 182), the difference in least squares mean for trough FEV_1 from baseline was -26 mL (95% CI -53 to 1 mL, p=0.573). There was a consistently lower mean trough FEV_1 in the ICS withdrawal group compared to the ICS continuation and the results were statistically significant until day 181.

Use of rescue medication
Use of rescue medication was presented differently in each study and no data were available for the WISDOM study. The mean percentage of rescue medication free days in the COSMIC study was 47% (SE 2%) in ICS withdrawal group and 53% (SE 2%) in the continuation group (p=0.014). In the INSTEAD trial the percentages of rescue mediation free days were 52.8% vs 54.6% (p=0.505) in the ICS withdrawal and continuation groups respectively. The mean change in puffs per day of rescue medication were -0.44 vs -0.49 respectively, with a difference of 0.05 (95% CI -0.17 to 0.28, p=0.650). In the SUNSET trial the difference in puffs per day between the two arms was 0.177 (95% -0.01 to 0.36) and the difference in rescue medication free days between the two arms was 0.103 (95% CI -3.25 to 3.25).

Dyspnoea
Dyspnoea scores on a scale of 0-4 were measured in the COSMIC study and there was a mean adjusted difference of 0.17 (SE 0.04) after 12 months. The modified Medical Research Council (mMRC) dyspnoea score was used to measure symptoms in the WISDOM study. At 12 months, the withdrawal group had an increase in mMRC score of 0.035 compared to a drop of 0.028 in the ICS continuation group. The Transitional Dyspnoea Index (TDI) was measured in the INSTEAD and SUNSET trials. The difference between the two groups was -0.12 (95% CI -0.71 to 0.48, p=0.694) in the total score measured via least squares mean after 26 weeks in the INSTEAD study with 68.7% and 69.4% of participants in the ICS withdrawal and continuation arms respectively achieving the MCID, OR 0.88 (95% CI 0.58 to 1.35, p=0.56). The difference between the two groups in the total score at 26 weeks in the SUNSET trial was -0.28 (95% CI -0.63 to 0.06).

Exercise capacity

Exercise capacity was not measured in any of the studies.

All-cause mortality
Overall, all-cause mortality was low in the three studies that reported it and there were no significant differences between the two groups. In the WISDOM study, the ICS withdrawal group had 43/1242 deaths (3.46%) and the ICS continuation group had 38/1243 deaths (3.06%) at the end of the study including the follow up period. At 26 weeks there were no deaths in the ICS withdrawal group and 2/288 deaths (0.69%) in the continuation group in the INSTEAD study. In the SUNSET study, the deaths were 4/527 (0.76%) and 5/526 (0.95%) in the ICS withdrawal and continuation groups respectively. The data were not pooled due to the low number of events.

Subgroup Analyses
Of the pre-specified subgroups to examine, data were only available for blood eosinophil counts in more than one study. These data were available in two studies (WISDOM and SUNSET). The most significant findings were when comparing baseline eosinophils of <300 cells·μL−1 to ≥300 cells·μL−1 on moderate or severe exacerbation rates between the ICS withdrawal and continuation groups.

In patients with eosinophil counts <300 cells·μL−1 there was no effect of ICS withdrawal of exacerbation rate, RR 1.03 (95% CI 0.90 to 1.18, p=0.71, I^2=0%) but there was a significant increase in exacerbations in patients with eosinophil counts ≥300 cells·μL−1, RR 1.63 (95% CI 1.24 to 2.14, p=0.0005, I^2=0%). Similar results were found when comparing baseline eosinophils of <2% vs ≥2%, RR 1.00 (95% CI 0.82 to 1.21, p=1.00, I^2=0%) vs RR 1.22 (95% CI 1.04 to 1.43, p=0.01, I^2=0%) respectively. There were no significant differences between the two groups on moderate or severe exacerbation rates when comparing baseline eosinophils of <150 cells·μL−1 or 150-299 cells·μL−1. The test for subgroup interaction was significant (p=0.02).

GRADE Evidence Tables

Author(s): Irena Laska, Marc Miravitlles, James Chalmers
Date:
Question: Withdrawal of inhaled corticosteroids compared to continuation of inhaled corticosteroids for COPD
Setting: Outpatients with COPD
Bibliography:

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	withdrawal of inhaled corticosteroids	continuation of inhaled corticosteroids	Relative (95% CI)	Absolute (95% CI)		
Frequency of moderate or severe exacerbations												
4 [1,2,3,4]	randomised trials	not serious	not serious	not serious	not serious	all plausible residual confounding would reduce the demonstrated effect	-/0	-/0	**Rate ratio 1.05** (0.98 to 1.12)	**-- per 1000 patient(s) per years** (from -- to --)	⨁⨁⨁⨁ HIGH	CRITICAL
Number of patients with at least one moderate or severe exacerbation												
2 [2,4]	randomised trials	not serious	not serious	serious [a]	not serious	none	157/477 (32.9%)	174/477 (36.5%)	**OR 0.84** (0.63 to 1.14)	**39 fewer per 1,000** (from 99 fewer to 31 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Time to first moderate or severe exacerbation												
3 [1,2,3]	randomised trials	not serious	not serious	not serious	not serious	none	-/0	-/0	**HR 1.04** (0.94 to 1.16)	**1 fewer per 1,000** (from 1 fewer to 1 fewer)	⨁⨁⨁⨁ HIGH	CRITICAL
Number of patients with at least one severe exacerbation												
1 [2]	randomised trials	serious [b]	not serious	serious [c]	not serious	none	1/293 (0.3%)	2/288 (0.7%)	**OR 0.49** (0.04 to 5.43)	**4 fewer per 1,000** (from 7 fewer to 30 more)	⨁⨁◯◯ LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	withdrawal of inhaled corticosteroids	continuation of inhaled corticosteroids	Relative (95% CI)	Absolute (95% CI)		
SGRQ												
4 [1,2,3,4]	randomised trials	not serious	not serious	not serious	not serious	none	0	0	-	MD **0.87 lower** (1.72 lower to 0.02 lower)	⨁⨁⨁⨁ HIGH	CRITICAL
Adverse events												
3 [1,2,3]	randomised trials	not serious	not serious	not serious	not serious	none	1447/2062 (70.2%)	1468/2057 (71.4%)	**OR 0.94** (0.82 to 1.08)	**13 fewer per 1,000** (from 42 fewer to 15 more)	⨁⨁⨁⨁ HIGH	CRITICAL
Pneumonia												
3 [1,2,3]	randomised trials	serious [d]	not serious	not serious	not serious	none	74/2062 (3.6%)	83/2057 (4.0%)	**OR 0.89** (0.64 to 1.22)	**4 fewer per 1,000** (from 14 fewer to 8 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Baseline eosinophils <2% on rate of moderate or severe exacerbations												
2 [1,3]	randomised trials	serious [e]	not serious	not serious	serious [f]	none	-/0	-/0	**Rate ratio 1.00** (0.82 to 1.21)	**-- per 1000 patient(s) per years** (from -- to --)	⨁⨁◯◯ LOW	CRITICAL
Baseline eosinophils >2% on rate of moderate or severe exacerbations												
2 [1,3]	randomised trials	serious [e]	not serious	not serious	serious [g]	none	-/0	-/0	**Rate ratio 1.22** (1.04 to 1.43)	**-- per 1000 patient(s) per years** (from -- to --)	⨁⨁◯◯ LOW	CRITICAL
Baseline eosinophils <150/microlitre on rate of moderate or severe exacerbations												
2 [1,3]	randomised trials	serious [e]	not serious	not serious	serious [f]	none	-/0	-/0	**Rate ratio 1.11** (0.93 to 1.31)	**-- per 1000 patient(s) per years** (from -- to --)	⨁⨁◯◯ LOW	CRITICAL
Baseline eosinophils 150-299/microlitre on rate of moderate or severe exacerbations												
2 [1,3]	randomised trials	serious [e]	not serious	not serious	serious [f]	none	-/0	-/0	**Rate ratio 1.03** (0.84 to 1.27)	**-- per 1000 patient(s) per years** (from -- to --)	⨁⨁◯◯ LOW	CRITICAL
Baseline eosinophils <300/microlitre on rate of moderate or severe exacerbations												
2 [1,3]	randomised trials	serious [e]	not serious	not serious	not serious	none	-/0	-/0	**Rate ratio 1.03** (0.90 to 1.18)	**-- per 1000 patient(s) per years** (from -- to --)	⨁⨁⨁◯ MODERATE	CRITICAL
Baseline eosinophils >300/microlitre on rate of moderate or severe exacerbations												
2 [1,3]	randomised trials	serious [e]	not serious	not serious	not serious	none	-/0	-/0	**Rate ratio 1.63** (1.24 to 2.14)	**-- per 1000 patient(s) per years** (from -- to --)	⨁⨁⨁◯ MODERATE	CRITICAL

CI: Confidence interval; **OR:** Odds ratio; **HR:** Hazard Ratio; **MD:** Mean difference

Explanations

a. Step down was to a single bronchodilator in both studies. It was difficult to extract data from the papers. The two larger studies did not report this end point.
b. The other three studies did not report this end point.

c. Step down was to a single bronchodilator.
d. Pneumonia was a rare event. The duration of the studies was too short or the studies had too few patient numbers to detect an effect.
e. Impact of baseline eosinophil levels on exacerbations in the WISDOM study was determined in a post-hoc analysis. Neither study stratified randomisation based on eosinophil levels at baseline.
f. The MCID for exacerbations in COPD is suggested to be 20%. This is exceeded by these data and may represent a clinically relevant difference.
g. Confidence intervals include only a 4% increase in exacerbations which would not be clinically meaningful.

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Final evidence to decision framework

Domain	Judgement	Research evidence Additional considerations
DESIRABLE EFFECTS	How substantial are the desirable anticipated effects? ○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know	Research evidence did not detect clinically meaningful differences in reduction of adverse events related to inhaled corticosteroids (ICS) withdrawal; however, it is expected that ICS withdrawal reduces steroid-related adverse events over the long-term in addition to a reduced medication burden, and better use of healthcare resources. It is acknowledged that some patients will not experience a benefit from ICS withdrawal while other patients may notice a substantial benefit.
UNDESIRABLE EFFECTS	How substantial are the undesirable anticipated effects? ○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know	Theoretically inhaled corticosteroid withdrawal could increase exacerbations, reduce lung function and reduce quality of life. In our analysis only quality of life was significantly reduced and this was substantially below the MCID.

	What is the overall certainty of the evidence of effects? ○ Very low ○ Low ● Moderate ○ High ○ No included studies	For the majority of endpoints the evidence is relatively consistent with low imprecision for exacerbation frequency for example, there are limited data available for analysis on endpoints such as FEV_1, hospitalizations and the studies are of relatively short duration. Overall certainty of the subgroup effects for eosinophils is low as there were even fewer studies and only one with eosinophil analysis as a pre-specified endpoint.
VALUES	**Is there important uncertainty about or variability in how much people value the main outcomes?** ○ Important uncertainty or variability ○Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability ○ No known undesirable outcomes	No research evidence included. The judgement reflects the guideline panel considerations. The analysis of important/critical outcomes showed a very high level of agreement on the importance of the selected outcomes. There is likely to be uncertainty and variability in interpretation of magnitude of effects. The guideline panel experience is that some clinicians and some patients interpret small changes in exacerbations, SGRQ or FEV_1 as important while others may not regard them as clinically significant. The patient perspective from the European Lung Foundation patient representative was that the majority of patients would give high value to exacerbations and symptoms with low value given the lung function changes in the absence of any impact on symptoms.
BALANCE OF EFFECTS	**Does the balance between desirable and undesirable effects favour the intervention or the alternative?** ○ Favours the alternative ○ Probably favours the alternative ○ Does not favour either the intervention or the alternative ● Probably favours the intervention ○ Favours the intervention ○ Varies ○ Don't know	The research evidence reveals that there is little difference in outcomes between either withdrawing or continuing ICS. There are uncertainties about the balance over the long-term due to the relatively short duration of studies. Based on the apparent lack of detrimental effects on exacerbations with the ICS withdrawal, the potential reduction of adverse events and treatment burden, the guideline panel considered that the overall balance favours the withdrawal of ICS in appropriate patients.

RESOURCES REQUIRED	How large are the resource requirements (costs)? ○ Large costs ○ Moderate costs ○ Negligible costs and savings ● Moderate savings ○ Large savings ○ Varies ○ Don't know	No research evidence included. The judgement reflects the guideline panel considerations. There are likely to be small cost savings associated with reduced ICS prescribing, but as these medications are not expensive in most healthcare systems, the savings are likely to be modest and patients will still be prescribed one or more inhalers.
EQUITY	What would be the impact on health equity? ○ Reduced ○ Probably reduced ● Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	No research evidence included. The judgement reflects the guideline panel considerations. We considered there would likely be no impact on health equity.
ACCEPTABILITY	Is the intervention acceptable to key stakeholders? ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	No research evidence included. The judgement reflects the guideline panel considerations. The majority of clinicians accept that unnecessary or inappropriate used medications should be withdrawn where they are not providing clinical benefits. The intervention is therefore likely to be acceptable among some but not all healthcare professionals. Feedback was provided by the European Lung Foundation patient advisor. The patients personal experience was that most patients would accept inhaled corticosteroid withdrawal where this was appropriate. Patients consider it important to avoid withdrawal in patients were this can result in harm and so they emphasise the importance of the subgroup data on blood eosinophils from a patients perspective.
FEASIBILITY	Is the intervention feasible to implement? ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	No research evidence included. The judgement reflects the guideline panel considerations. Yes. Prescription of inhaled medications is already standard of practice and monitoring can be done in standard healthcare settings.

Should inhaled corticosteroids be withdrawn in patients with COPD and a low frequency of exacerbations?					
TYPE OF RECOMMENDATION	**Strong** recommendation **against** the intervention ○	**Conditional** recommendation **against** the intervention ○	Conditional recommendation for either the intervention or the alternative ○	**Conditional** recommendation **for** the intervention ●	**Strong** recommendation **for** the intervention ○
RECOMMENDATION	1) For patients with COPD without a history of frequent exacerbations consider ICS withdrawal (conditional recommendation, moderate quality of evidence) and measure blood eosinophil count to help decision-making. 2) We recommend <u>not</u> to withdraw ICS in patients who have a blood eosinophil count ⩾300 eosinophils·μL−1, with or without a history of frequent exacerbations (strong recommendation, moderate quality of evidence). 3) For patients with COPD and a history of frequent exacerbations but <300 eosinophils·μL−1, no recommendation can be formulated 4) If ICS are withdrawn, patients should be treated with one or two long-acting bronchodilators (strong recommendation, moderate quality of evidence). Note that patients without a history of frequent exacerbations are those with no more than one moderate exacerbation in the previous year.				
JUSTIFICATION	This recommendation is based on the evidence identified which showed no increase in exacerbations or clinically significant deterioration in symptoms following inhaled corticosteroid withdrawal. We have limited the recommendation to patients with infrequent exacerbations as patients in the majority of the trials were infrequent exacerbators (0-1 in the previous 12 months) apart from the COSMIC study. Also it has been suggested in well-designed, larger and longer trials assessing efficacy of ICS and inhaled bronchodilators that outcomes are superior with ICS use in frequent exacerbators (<u>≥</u> 2 per year). We recommended stepping down to bronchodilator therapy as the two larger trials (WISDOM and SUNSET) stepped down to dual therapy and included patients with moderate to severe COPD, where dual therapy has been proven to be more efficacious than single bronchodilator therapy. The recommendations regarding eosinophil subgroups are based on the evidence presented in “subgroup considerations” below.				
SUBGROUP CONSIDERATIONS	Subgroup data for baseline eosinophil counts suggest an important subgroup effect on exacerbations, which is reflected in the recommendations above. There were insufficient data to perform meaningful subgroup analyses on the other pre-specified subgroups of interest, particularly past history of exacerbations and baseline FEV_1. The studies used a single eosinophil count at baseline and the evidence suggests that this is sufficient to guide withdrawal. Pragmatically the panel acknowledges that multiple historic eosinophil counts may be available in daily clinical practice. Where multiple eosinophil				

	counts measured during clinical stability are available and below 300 cells·μL−1, this would increase confidence in ICS withdrawal.
IMPLEMENTATION CONSIDERATIONS	Three studies stopped ICS abruptly while one study withdrew gradually. The absence of meaningful differences in outcomes between these studies suggests that ICS can be abruptly withdrawn in the majority of cases.
MONITORING AND EVALUATION	Some patients may deteriorate following any change in treatment, including ICS withdrawal. Therefore monitoring of exacerbation frequency, symptoms and lung function is recommended.
RESEARCH PRIORITIES	Further trials with larger numbers of patients that include subgroup analyses, such as those mentioned above, are required.