Introduction

Chronic obstructive pulmonary disease (COPD) is a common disorder, which has a large negative effect on health-related quality of life (1) and causes a large burden for the individual patient and the society as a whole (2). COPD is globally the third leading cause of mortality (3) and in Sweden it has been estimated that COPD patients on average live 8 years shorter than aged matched persons without COPD (4).

COPD is characterised by chronic airflow obstruction. In the GOLD guidelines, airflow obstruction is defined as a ratio between forced expiratory volume in one second (FEV₁) and forced vital capacity (FVC) that is below 0.7 after bronchodilation (5). The Burden of Obstructive Lung Disease (BOLD) study showed that globally 10–20% of the population that are 40 years or older have a spirometry that fulfils this criterion for COPD (6). A problem, however, is that 80% of these individuals have not been diagnosed (7). There is also the opposite problem. In the BOLD study, half of those diagnosed as having COPD did not fulfil the spirometric criteria for the disease (8).

Abstract: In chronic obstructive pulmonary disease (COPD), treatment with inhaled corticosteroids (ICSs) in combination with long acting beta-2-agonists (LABA) or LABA/long-acting muscarinic antagonists (LAMA) is used in order to reduce exacerbations. Treatment with ICS is, however, associated with side effects such as oropharyngeal candidiasis, skin thinning or easy bruising and pneumonia. The aim of this review was to investigate when to use ICS in COPD and to compare the effectiveness and safety of different ICSs. Studies comparing the effect of ICS/LABA and LABA/LAMA on exacerbations have shown divergent results, whereas most studies comparing ICS/LABA/LAMA (triple therapy) with LABA/LAMA have reported fewer exacerbations with triple therapy. Several investigations have shown that the number of eosinophils in blood predicts whether a patient will benefit from treatment with ICS. There is also data indicating that ICS has a small but significant positive effect on lung function decline and decrease mortality. There are four observational studies showing a better effect on exacerbations with budesonide/formoterol than fluticasone propionate/salmeterol and three observational studies showing less risk of pneumonia with budesonide than fluticasone propionate. Studies comparing the effect and safety of other ICSs such as fluticasone furoate and beclomethasone are too few to draw firm conclusions from. In conclusion, ICS together with LABA or LABA/LAMA reduces the risk of exacerbations in COPD. The indication of using ICS in COPD is stronger if the patient has increased blood eosinophils levels. There are data indicating that the choice of ICS matters, with studies showing a better effect-safety profile with budesonide compared to fluticasone propionate whereas it is not possible to make benefit-risk comparisons between the other licensed ICSs.

Keywords: Chronic obstructive pulmonary disease (COPD); inhaled corticosteroids (ICSs); eosinophils

Review Article

Treatment with inhaled corticosteroids in chronic obstructive pulmonary disease

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Abstract: In chronic obstructive pulmonary disease (COPD), treatment with inhaled corticosteroids (ICSs) in combination with long acting beta-2-agonists (LABA) or LABA/long-acting muscarinic antagonists (LAMA) is used in order to reduce exacerbations. Treatment with ICS is, however, associated with side effects such as oropharyngeal candidiasis, skin thinning or easy bruising and pneumonia. The aim of this review was to investigate when to use ICS in COPD and to compare the effectiveness and safety of different ICSs. Studies comparing the effect of ICS/LABA and LABA/LAMA on exacerbations have shown divergent results, whereas most studies comparing ICS/LABA/LAMA (triple therapy) with LABA/LAMA have reported fewer exacerbations with triple therapy. Several investigations have shown that the number of eosinophils in blood predicts whether a patient will benefit from treatment with ICS. There is also data indicating that ICS has a small but significant positive effect on lung function decline and decrease mortality. There are four observational studies showing a better effect on exacerbations with budesonide/formoterol than fluticasone propionate/salmeterol and three observational studies showing less risk of pneumonia with budesonide than fluticasone propionate. Studies comparing the effect and safety of other ICSs such as fluticasone furoate and beclomethasone are too few to draw firm conclusions from. In conclusion, ICS together with LABA or LABA/LAMA reduces the risk of exacerbations in COPD. The indication of using ICS in COPD is stronger if the patient has increased blood eosinophils levels. There are data indicating that the choice of ICS matters, with studies showing a better effect-safety profile with budesonide compared to fluticasone propionate whereas it is not possible to make benefit-risk comparisons between the other licensed ICSs.

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The underlying cause for the lung impairment in COPD is airway inflammation and destructive structural changes (9). This inflammation includes both the innate and adaptive immune system and many kinds of cells such as neutrophils, macrophages and lymphocytes. Lately it has become clear that the eosinophil granulocyte also is an important player in the inflammatory pattern of COPD (10). Even though inflammation is an underlying mechanism in COPD, the role of anti-inflammatory treatment with inhaled corticosteroids (ICSs) is much more limited in COPD (5) than it is for asthma (11).

The aim of this review was to investigate when ICS should be used in COPD and also to compare different ICSs when it comes to effectiveness and safety in COPD treatment.

Methods

This is a narrative review investigating the effect of ICS in COPD. The focus of the review is on five topics:

(I) The effect of ICS in combination with long acting β2-agonists (LABA) or LABA/long acting muscarinic antagonists (LAMA) on exacerbations;
(II) The predictive value of measuring blood eosinophil (B-Eos) levels on the effectiveness of ICS in COPD;
(III) The effect of ICS on lung function decline and mortality in COPD;
(IV) Interclass difference between ICSs in effectiveness and safety in COPD;
(V) Does the benefit of using ICS outweigh the negative side effects?

Results

Treatment with ICS in COPD

Treatment with ICS in combination with LABA or LABA/LAMA is in COPD is mainly used in order to reduce the risk of exacerbations (12). It should, however, be noted that treatment with ICS in COPD may have other positive effects such as increasing health-related quality of life (13,14), improving dyspnoea (14) and sleep (15,16). There are also studies suggesting that COPD patients using ICS have a lower risk of cardiovascular disease (17) and lung cancer (18,19) than COPD patients not using ICS. Treatment with ICS is, however, also associated with side-effects, where the most established ones are oropharyngeal candidiasis, skin thinning or easy bruising (20) and pneumonia (21-24). Other possible but less established side effects are cataract, diabetes and osteoporosis (20). These side-effects together with the fact that treatment with LAMA or LABA/LAMA to some extent also reduce the risk of exacerbations (25,26) have led to the use of ICS in COPD being questioned (27).

Studies comparing ICS/LABA with LABA, LAMA or LAMA+LABA

Adding an ICS to a LABA has repeatedly been shown to improve airflow limitation, quality of life, and exacerbation rates compared with use of a LABA alone in randomised controlled trials (RCT) (13,28,29). Treatment with ICS/LABA and LAMA was studied in one RCT. No difference in exacerbation rate was found when treatment with fluticasone propionate/salmeterol (FP/SALM) and tiotropium was compared (30). There was, however, a significantly lower rate of exacerbations requiring systemic corticosteroids, lower mean St George Respiratory Questionnaire score (better health-related quality of life) and lower mortality in the FP/SALM group.

Patients treated with LABA/LAMA (indacaterol/glycopyrronium) had a lower incidence of exacerbations than patients treated with FP/SALM in two RCTs (31,32). Recently, however, two studies have shown the opposite results with ICS/LABA being superior to LABA/LAMA in term of exacerbations (14,33). Differences in patient selection may be an explanation to these diverging results. Another explanation may be differences in the intrinsic activity of the molecules used in the studies. FP was the ICS used in the studies showing superiority for LABA/LAMA while fluticasone furoate and budesonide (BUD), respectively were used in the two studies showing a better effect of ICS/LABA.

Triple therapy

Combining all three classes of drugs (ICS/LABA/LAMA), so called triple therapy, has been investigated in many studies. In two studies patients treated with BUD/formoterol (FORM) + tiotropium had less exacerbations than patients treated with tiotropium alone (34,35). No difference in exacerbation rate was found between treatment with FP/SALM + tiotropium vs. tiotropium in two other RCTs although a benefit for triple therapy compared to LAMA was found for other outcome variables (36,37).
Recently fixed triple combinations have been introduced. In three studies, patients on fixed triple compounds had a lower incidence of exacerbations than patients using LABA/LAMA or ICS/LABA (14,33,38). In one of these studies, triple therapy was also shown to increase health-related quality of life and decrease dyspnoea to a greater extent than LABA/LAMA or ICS/LABA treatment (14).

**Asthma COPD overlap (ACO)**

Many COPD patients have concomitant asthma and the term ACO has been introduced to cover this condition (39,40). Patients with ACO have more symptoms and more exacerbations than patient with only asthma or COPD (39,41). There is lack of studies evaluating treatment of ACO, but it is generally recommended that this treatment should include ICS (42,43).

**Eosinophils**

Several studies have shown that B-Eos predicts whether a patient will benefit from taking ICS in combination with LABA or LABA/LAMA compared with bronchodilators alone (33,44-50) (Table 1). Different thresholds have been used and in some studies B-Eos have been expressed as percentage of the total leukocyte count, whereas in the more recent studies the number of eosinophils per volume blood has been used. In all studies the benefit of using ICS in combination with long acting bronchodilators increases in comparison with only using long acting bronchodilators with the number of eosinophils, so the context of threshold levels is relative. Based on the studies above, GOLD strongly support the use of ICS in combination with LABA or LABA/LAMA in COPD patients with frequently exacerbation and B-Eos >0.3×10⁹/L, consider use of ICS in combination with LABA or LABA/LAMA when B-Eos are between (0.1–0.3)×10⁹/L while ICS is not at all recommended if B-Eos is <0.1×10⁹/L (51). The risk was further increased if these patients were using ICS.

**Effect of ICS on lung function decline**

COPD is characterised by a faster than normal decline in lung function (52). There were expectations that treatment with ICS would slow the speed of this decline. Several early studies failed to show this (53-55). In some more recent studies, however, a small positive effect on lung function decline with ICS (8–13 mL/years) has been reported (56,57). In one study, the effect of ICS on lung function decline was only found in COPD patients with B-Eos ≥2% (58).

### Table 1 Blood eosinophils (B-Eos) as biomarker for predicting response to ICS in COPD

| Study          | Treatment                                                                 | B-Eos threshold | Effect                                           |
|----------------|---------------------------------------------------------------------------|-----------------|--------------------------------------------------|
| Pascoe 2015 (47) | Fluticasone furoate/vilanterol vs. vilanterol                             | ≥2%             | Less exacerbations with ICS/LABA than LABA       |
| Siddiqui 2015 (48) | Beclomethasone/formoterol vs. formoterol                                   | ≥0.3×10⁹/L      | Less exacerbations with ICS/LABA than LABA       |
| Wedzicha 2016 (32) | FP/SALM vs. indacaterol/glycopyrronium                                     | ≥2%             | No difference in exacerbations                   |
| Watz 2016 (49)   | FP/SALM + tiotropium vs. SALM + tiotropium                                 | ≥4% or 0.3×10⁹/L| Less exacerbations with triple than LABA/LAMA    |
| Bafadhel 2018 (45) | BUD/FORM vs. FORM                                                          | ≥0.3×10⁹/L      | Less exacerbations with ICS/LABA than LABA       |
| Chapman 2018 (50) | FP/SALM + tiotropium vs. indacaterol/glycopyrronium                      | ≥0.3×10⁹/L      | Less exacerbations with triple than LABA/LAMA    |
| Ferguson 2018 (33) | BUD/FORM/glycopyrronium vs. formoterol/glycopyrronium                    | ≥0.3×10⁹/L      | Less exacerbations with triple than LABA/LAMA    |
| Pascoe 2019 (46) | Fluticasone furoate/vilanterol/umeclidinium vs. vilanterol/umeclidinium  | ≥0.3×10⁹/L      | Less exacerbations with triple than LABA/LAMA    |

ICS, inhaled corticosteroids; COPD, chronic obstructive pulmonary disease; LABA, long acting β₂-agonists; LAMA, long-acting muscarinic antagonist; FP, fluticasone propionate; SALM, salmeterol; BUD, budesonide; FORM, formoterol.
Effect of ICS on mortality

Studies investigating whether treatment with ICS influences all-cause mortality are summarized in Table 2. In a retrospective study, based on primary care data from the United Kingdom Soriano and co-workers found that patients treated with FP/SALM and FP had lower mortality than matched patients that were not on ICS and LABA (59). In the only RCT where mortality was the primary outcome variable, patients treated with FP/SALM had an almost statistically significant better survival than patients on placebo did (P=0.052) (29). In another study, FP/SALM treated patients had better survival than patients treated with tiotropium (30). A pooled analysis of two RCTs showed that BUD treated patients had better survival than non-BUD treated patients (60). In a RCT that included patients that had both COPD and cardiovascular disease, no difference was found in survival when comparing those with fluticasone furoate/vilanterol with those with placebo (56). Finally, in the IMPACT study, patients with triple therapy (fluticasone furoate/vilanterol/umeclidinium) and ICS-LABA (fluticasone furoate/vilanterol) had less all-cause mortality than those treated with LABA/LAMA (vilanterol/umeclidinium) (14).

Comparison of different ICS

There are many ICSs to choose between in the treatment of COPD. There are, however a lack of RCTs that compare these different ICSs in COPD. Fortunately, there are data available from observations studies. Most of these studies have compare the effectiveness and safety of BUD with that of FP. Unfortunately, there are only a few studies that compare these two ICS with other ICS such as fluticasone furoate or beclomethasone.

Effect on exacerbations

Four retrospective studies have found a lower exacerbation rate in COPD patients treated with BUD/FORM compared to those treated with FP/SALM (Table 3). The first of these studies was a Canadian study were approximately 1,300 patients treated with BUD/FORM was matched with the same number of patients treated with FP/SALM. The study period was one year (61). In the study, the risk of all kinds of exacerbations was 15–39% lower in patients using BUD/FORM than in those using FP/SALM. Similar results were found in studies from Sweden (41), Italy (63) and Taiwan (64). The only study where no difference was found between BUD/FORM and FP/SALM was from the United States and its possible that this was related to low adherence to prescribed medication in that study (62). No difference in acute severe exacerbations was found between FP/SALM and beclomethasone/FORM in an observational study from Taiwan (65).

Risk of pneumonia

In the PATHOS study, data from electronic medical records were merged with Swedish national registry data. COPD patients on FP/SALM had more pneumonia events than matched patients with BUD/FORM [rate ratio (95% CI) 1.73 (1.57-1.90)] (66). Similar results were found in a study from Taiwan (64). Use of FP was associated with
highly increased risk of pneumonia in a large Canadian database study [rate ratio (95% CI) 2.01 (1.93–2.10)], whereas the association was lower for the use of BUD [rate ratio (95% CI) 1.17 (1.09–1.26)] (67). In an analysis of the UPLIFT trial, the incidence of pneumonia was higher in patients using FP than those using other ICS (68). Finally, a tendency to a higher risk of pneumonia was found in patients treated with FP/SALM than those using BUD/FORM in an analysis of hospitalised COPD patients in Japan (69). The difference between FP and BUD in the association to pneumonia has also been highlighted in meta-analyses (23,24,70). In one of these analyses, Kew et al. found that the risk of any pneumonia event was higher with fluticasone than with BUD (OR 1.86, 95% CI: 1.04 to 3.34). However, they also stated that this finding should be interpreted with caution because of possible differences in the assignment of pneumonia between the studies (70).

ICS, inhaled corticosteroids; LABA, long acting β2-agonists; BUD, budesonide; FORM, formoterol; FP, fluticasone propionate; SALM, salmeterol; RR, risk ratio; ED, emergency department; IRR, incidence rate ratio; OCS, oral corticosteroids.

Table 3: Studies comparing the effect of different ICS-LABA combinations on exacerbations

| Study     | Treatment              | Follow-up time | Effect                                      |
|-----------|------------------------|----------------|---------------------------------------------|
| Blais 2010 (61) | BUD/FORM vs. FP/SALM | 1 year         | Less exacerbations with BUD/FORM            |
| Larson 2013 (41) | BUD/FORM vs. FP/SALM  | Up to 10 years | Less exacerbations with BUD/FORM            |
| Kern 2015 (62)  | BUD/FORM vs. FP/SALM  | 1 year         | No difference                              |
| Perrone 2016 (63) | BUD/FORM vs. FP/SALM | Up to 3 years  | Less exacerbations with BUD/FORM            |
| Yang 2017 (64)   | BUD/FORM vs. FP/SALM  | Up to 13 years | Less exacerbations with BUD/FORM            |

ICS, inhaled corticosteroids; LABA, long acting β2-agonists; BUD, budesonide; FORM, formoterol; FP, fluticasone propionate; SALM, salmeterol; RR, risk ratio; ED, emergency department; IRR, incidence rate ratio; OCS, oral corticosteroids.

benefits of using ICS versus side effects

Using ICS in combination with LABA and LABA/LAMA have clinical important beneficial effects and negative side effects. It is therefore important to decide if the benefits outweigh the negative effects. In the PATHOS study, the incidence of exacerbations was about ten times higher than the incidence of pneumonia (41,66). This indicates that the preventive effect of exacerbations is more important than the risk increase in pneumonia. On the other hand, Suissa and co-workers calculated number needed to treat (NNT) for exacerbations and pneumonia (74) based on a 1-year trial of FP/SALM vs. SALM (15). They found that the NNT for avoiding one exacerbation during one year of treatment with FP/SALM was relatively similar as the NNT for inducing one pneumonia (14 vs. 20) (74). In a
review from 2018, Agustí et al. conclude that that some COPD patients benefit from the addition of ICS to long-acting bronchodilator treatment whereas others do not and that the risk/benefit ratio of adding ICS has to be carefully considered in each individual patient (43). Factors that support using ICS are repeated exacerbations, B-Eos $\geq 0.3 \times 10^9/L$ and concomitant asthma, whereas repeated pneumonia, history of mycobacterial infections and B-Eos $<0.1 \times 10^9/L$ support avoiding to use ICS (43).

**Conclusions**

ICS together with LABA or LABA/LAMA reduces the risk of exacerbations in COPD. ICS, however, do have side effects where an increased risk of pneumonia is probably the most clinically important one. The indication of using ICS in COPD is stronger if the patient has concomitant asthma and/or increased B-Eos levels. Apart from reducing the risk of exacerbations, there is also data indicating that ICS has a small but significant positive effect on lung function decline and mortality. Overall the benefits of ICS in treating COPD continue to outweigh their risks, however, the choice of ICS matters with data from observational studies showing a better effect-safety profile with BUD compared to FP whereas it is not possible to make benefit-risk comparisons between the other licensed ICSs.

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**Footnote**

Conflicts of Interest: The author has received payments for educational activities from AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Novartis and Teva, and has served on advisory boards arranged by AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Novartis and Teva.

Ethical Statement: The author is accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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