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REVIEW

Inhaled Corticosteroids in COPD: Trying to Make a Long Story Short

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Abstract: The use of inhaled corticosteroids (ICSs) in long-term treatment of COPD has been a debated topic for a long time. According to the evidence produced till now, ICSs are presently advocated in combination with long-acting bronchodilators for high-risk symptomatic COPD patients with a history of frequent COPD exacerbations. However, the heterogeneity of COPD patients in terms of prevalent underlying disease, with its associated biological and functional characteristics, and different types of exacerbation makes this recommendation highly questionable. This review aims to discuss the usefulness of ICSs in the pharmacological management of COPD and trys to detect those aspects that may likely anticipate a beneficial response following their therapeutic use related to respiratory function, functional decline, prevention of exacerbation, and quality of life. In this respect, the BERN acronym, meaning Bronchiolitis, Eosinophilia, Responsiveness to bronchodilator, and Non-smoker, may be of practical utility to select among COPD patients those that can take more advantage from ICS adoption when positive and vice versa when negative.

Keywords: inhaled corticosteroids, COPD, COPD exacerbations, BERN

Background

Presently, there are widespread, evidence-based, expert recommendations about inhaled corticosteroid (ICS) use in patients suffering from COPD suggesting their adoption in the chronic treatment of COPD combined with long-acting bronchodilators when in symptomatic patients pulmonary function is halved (ie, postbronchodilator FEV_1 <50%–60% predicted) and/or frequency of COPD-related acute exacerbations (AECOPDs) is two or more episodes per year or in the presence of at least one severe AECOPD per year in the previous year/s.[1] These recommendations stem from evidence that has been produced from randomized controlled trials (RCTs) where recruitment of large cohorts of patients had simply required an age >40 years, smoking history >10 pack/years, and FEV1/FVC ratio <70% after acute administration of bronchodilators and no self-reported asthma.

Apart from three historical RCTs looking at annual FEV_1 decline rates in COPD patients suffering from moderate airflow obstruction treated with ICSs alone,[2–4] all COPD patients enrolled in more recent RCTs have had moderate–severe airflow obstruction (usually with mean postbronchodilator FEV_1 around 50% of predicted), and for AECOPD reduction as outcome, a history of one or rarely two or more AECOPDs reported in the previous year.[5–8]

Within this framework (for the last 20 years), ICSs alone or more often in combination with bronchodilators (long-acting β_2 agonists [LABAs]) compared to

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placebo or bronchodilators (LABAs) did not significantly reduce overall mortality or appreciably the mean FEV_1-decline rate, but were able to give some improvement in lung function, sometimes associated with lesser symptoms and greater exercise tolerance, better quality of life, and a reduction in AECOPDs of 25%–40% vs placebo and almost invariably of about 20%–30% vs LABAs.[9] Considering the well-recognized heterogeneity of COPD patients, going from the underlying prevalent disease (ie, fibrosing chronic bronchiolitis alone versus fibrosing chronic bronchiolitis plus centrilobular emphysema, from mild to advanced, versus panlobular emphysema), to the different nature of AECOPDs (eg, from infective to eosinophilic, pauci-inflammatory, comorbidity-related), the aforementioned evidence appears limited and coarse.[10]

In the era of targeted or even personalized therapy, it seems really illogical in COPD to deny ICSs (if useful) until 50% of lung function has been lost, or in contrast, to advocate ICSs in the presence of frequent, but noneosinophilic AECOPDs, trying to prevent them. This may lead to the confusion that is only going to increase among general practitioners and specialists, leading to the opposite result, ie, to give the same treatment to everybody.[11] The future challenge in order to build helpful evidence is to find useful and practical biomarkers (clinical, functional, biological, radiological, omic) to select COPD patients accurately who deserve ICSs in combination with one or two bronchodilators. Until then, it might be interesting for the reader to take in current knowledge about ICSs in COPD in terms of why, what, who, and when.

Why

The relatively few data we have about the activity of ICSs in COPD patients from bronchial biopsies, induced sputum, or bronchoalveolar lavage (BAL) — biological windows of proximal, large, or small airways, respectively — have demonstrated many anti-inflammatory and immunomodulatory effects. In a meta-analysis published in 2012, four studies using bronchial biopsies (n=102 participants with COPD) showed a significant reduction in $CD4^+$ and $CD8^+$ lymphocyte counts with no effect in neutrophils in bronchial walls, and in five studies using BAL (n=309 participants with COPD) a significant reduction in both lymphocyte and neutrophil counts at the epithelial surface of more peripheral airways with ICSs vs placebo.[12]

Although these findings may be influenced by the current smoking status of patients and concomitant use of other drugs, such as bronchodilators and theophylline, they firmly suggest that ICSs essentially downregulate lymphocytic inflammation and adaptive immunity that become predominant in the later stages of COPD. In addition, ICS or oral CS use has been associated with lower occurrence of lymphoid follicles in small airways, which tends to increase with progression of airflow obstruction: <5% in GOLD stages 1 and 2, and >30% in GOLD stages 3 and 4.[13]

Data on eosinophils for both bronchial biopsies and BAL were controversial and overall not significant using ICSs vs placebo.[12] Another meta-analysis on six studies looking at the effects of ICSs on inflammatory cells in induced sputum (n=162 participants with COPD) showed a reduction in lymphocyte and neutrophil counts, with on average no change in eosinophils.[13] The conflicting and surprising data about the ICS effect on eosinophils, with both positive and negative results in COPD, could be related to the unselected recruitment of the patients. We know that only a third of COPD patients have a persistent and relevant eosinophilic airway inflammation, as documented by induced sputum and BAL, and likely only these COPD patients may respond to ICSs treatment in terms of eosinophil reduction and related benefit.[14,15] In fact, in subgroups of stable COPD patients with high eosinophilic counts in sputum, the adoption of ICSs on top of bronchodilators has produced greater functional improvement in terms of FEV_1 increase and better quality of life in terms of St George's Respiratory Questionnaire score reduction than other subgroups of COPD patients with lower eosinophilic counts in the sputum.[16] The same results were observed in nonsmoking COPD patients with high levels of exhaled FeNO, which are usually associated with eosinophilic airway inflammation.[17]

It is important to say that such immunomodulatory and anti-inflammatory effects after long-term treatment with ICSs appear significant compared with placebo in sputum, BAL, and bronchial biopsies, mostly in nonsmoking (never-smokers or ex-smokers) than in smoking COPD patients.[18] Oxidative and nitrative stress in COPD patients is high, and in those who smoke it is higher than in nonsmoking COPD patients. Although a bit controversial, it is believed that because of the oxidative/nitrative-induced HDAC2 inactivation in smoking COPD patients, ICSs cannot exert their genomic actions.[19] This may explain the so-called ICS resistance of COPD-related inflammation, which can be partly reversed by stopping smoking or avoiding the HDAC2 inactivation through antioxidant drugs and low-dose theophylline and experimentally by PI3Kδ inhibitors. In any case, current

smoking greatly reduces the aforementioned biological effects of ICSs.

Interestingly, in a small cohort of moderate–severe COPD patients (n=32 participants), long-term treatment with ICSs induced partial changes in extracellular matrix composition of the bronchial wall by increasing both proteoglycans and collagen I and III deposition (versican and collagen III significantly vs placebo). These modifications might reduce the compliance of the bronchial walls by modulating airway remodeling and increase lung function by preventing small-airway collapse.[20] All these effects can offer a biological explanation for the favorable response to ICSs observed in some subgroups of COPD patients, where ICSs together with bronchodilators might actually represent a disease-modifying drug, able to control a relevant part of underlying inflammation and its consequences: symptoms, mechanical impairment, functional decline, a number of AECOPDs, quality of life, and perhaps all-cause mortality.[21]

What

Chronic Bronchiolitis Versus Pulmonary Emphysema

Small-airway inflammation and remodeling with progressive peribronchiolar fibrosis, namely fibrosing chronic bronchiolitis, represents the most common disease underlying COPD, because of the extensive small-airway resistance increase. In contrast, few COPD patients suffer from panlobular emphysema as the initial underlying cause of chronic airflow reduction. With natural progression of small-airway disease involving the respiratory intra-acinar bronchioli, very often the associate development of another form of emphysema starting from the center of secondary lobule, so-called centrilobular emphysema, is observed that can progress from mild to moderate, confluent, and finally advanced form, according to the extent of diseased lung.[22]

In mild–moderate COPD (GOLD stages 1 and 2), air trapping in the diseased lung is almost entirely due to chronic bronchiolitis, while in more severe COPD (GOLD stages 3 and 4) this is largely caused by associated centrilobular emphysema that progressively increases, as elegantly shown by parametric response–mapping computed tomography (CT)-scan studies.[23] That means that abnormal lung inflation in the early phase of COPD is essentially "functional" (disappearing at full inspiration) due to the decreased caliber of small airways, while in the latter COPD is also "anatomical" (remaining at full inspiration), because of irreversible destruction of alveolar septa. Therefore, the main determinants of airflow obstruction change from increased small-airway resistance to expiratory small-airway collapse and loss of elastic recoil with progression of COPD severity.

It is logical that the anti-inflammatory and immunomodulatory effects of ICSs in combination with bronchodilators are most useful when the prevalent underlying disease is still chronic bronchiolitis (mild–moderate COPD) in the attempt to control and avoid the harmful consequences of adaptive immunity on airway remodeling and peribronchiolar alveolar septa damage subsequent to the recruitment and activation of $CD4^+$ and mainly $CD8^+$ lymphocytes. In contrast, when the prevalent disease has become centrilobular emphysema, especially if confluent or advanced (severe–very severe COPD), antiapoptotic activity on neutrophils of ICSs[24] should represent a contraindication to their use, due to the risk of further progression of alveolar septa digestion by the uncontrolled protease burden typically associated with this type of inflammation. This has been proved by the GLUCOLD study, an RCT with a 30-month follow-up performed in a cohort of 114 COPD patients (64 current smokers) with no history or diagnosis of asthma, which aimed to assess the pathological and clinical efficacy (and their link) of long-term treatment with ICSs. These patients were characterized by moderate airflow obstruction
(mean FEV_1=56% predicted), but with almost normal lung diffusion capacity (mean K_{CO} =73% predicted), presence of airway hype-responsiveness, and some degree of bronchial responsiveness (mean ΔFEV_1 =7% of predicted postbronchodilator).

In the arms treated with fluticasone alone or in combination with salmeterol, the mean FEV_1-decline after 2.5 years was +7 mL/year and -16 mL/year, respectively, vs -79 mL/year for the placebo arm (p<0.001).[25] These findings clearly show that in COPD patients affected substantially by chronic bronchiolitis, ICSs can attenuate or even stop their functional decline in association with a decrease in airway inflammation, as documented by the reduction in inflammatory cell counts ($CD4^+$ and $CD8^+$ lymphocytes and mast cells) on bronchial biopsies at 6 and 30 months. A subanalysis of this study aimed to identify predictors of best response to ICSs in terms of FEV_1 decline after 30 months compared to placebo, found that COPD patients who initially had higher DL_{CO} (>65% predicted), lower air trapping (residual volume/total lung capacity ratio <42%), lower sputum inflammatory-cell total count (<169×10/mL cell), and fewer pack-years (<42) exhibited attenuated or no functional loss if actively treated.[26] In other

words, COPD patients benefit much more from long-term treatment with ICSs if they have less severe airway inflammation, no or mild emphysema, lower pulmonary hyperinflation, and lower smoking history.

In addition, an insightful prospective observational study performed in >200 Japanese COPD patients (Hokkaido COPD cohort study) aged 69 years on average who were treated with usual therapy, including ICSs, and followed for 5 years showed unequivocally that in those with chronic bronchiolitis with or without mild associated emphysema (indicated by the normal or nearly normal CT-scan lung densitometry and mean K_{CO} > 70% predicted), no change in FEV_1 was observed (no decliners). In contrast, those with a substantial presence of pulmonary emphysema on CT-scan quantitative analysis and lowest K_{CO} (<60% predicted) had a markedly abnormal FEV_1-decline rate, irrespective of any treatment (fast decliners). In those patients with an intermediate extent of pulmonary emphysema and K_{CO} values, the rate of FEV_1 decline was similar or slightly greater than what is expected in normal controls of the same age range (slow decliners).[27]

Chronic Eosinophilic Bronchiolitis

Many studies have shown that in COPD patients (about 20%–35%) with no history or diagnosis of asthma, persistent eosinophilic inflammation is found in sputum with eosinophilic values ≥3% of total inflammatory cell numbers.[28,29] In the bronchial and bronchiolar epithelial cells of these COPD patients, increased upregulation and expression of proinflammatory gene–driven type 2 inflammation has been found in response to noxious stimuli, associated with significant better respiratory functional response to ICSs vs placebo.[30–32] It is highly plausible that these COPD patients may frequently have AECOPDs with raised levels of eosinophils in sputum (>2%) and in blood[33] that respond better to systemic corticosteroids without need of antibiotics[34] and can be more effectively prevented by long-term treatment with ICSs combined with bronchodilators.

A post hoc analysis of several trials and recent data of prospective RCTs aimed to assess the ability of treatment with ICSs in combination with ultra-LABAs and ultra-LABAs + ultra-long-acting muscarinic antagonists to prevent AECOPDs in COPD patients with frequent exacerbations showed that the presence of ICSs decreased the annual rate of AECOPDs in terms of initial percentage or absolute number of eosinophils in blood measured in stable conditions, with a clear dose–response curve:[35–41] no effect below 2% or 100–150 elements per 100 μL of blood, and much greater effect above 4% or 300–350 elements per 100 μL of blood.[42]

Presently, high eosinophil counts in the blood of stable COPD patients who frequently exacerbate is considered a biomarker of positive response to ICSs in preventing AECOPDs (likely eosinophilic),[43] with a cut off of 300–350 elements per 100 μL of blood that is less sensitive, but markedly more specific, with highest positive predictive power.[44] In addition, a recent post hoc analysis of data collected in the ISOLDE trial where COPD patients (mean FEV_1 50% predicted) were randomly treated with ICSs alone or placebo to assess ICS effect on lung-function decline during a 3-year follow-up, showing no effect of active treatment in the overall COPD population, has provided very interesting results. After division of the patients according to initial percentage of blood eosinophils, compared to placebo subgroups those with >2% blood eosinophils did not show any postbronchodilator FEV_1 decline during follow-up. In contrast, no effect, with a similar rate of FEV_1 decline observed with placebo, was found in those with <2% blood eosinophils.[45] Within the limits of a post hoc analysis and the choice of a 2% cutoff, these findings strongly suggest that ICS treatment in stable COPD patients with blood eosinophilia may significantly attenuate or even stabilize their functional decline rate, even in those with moderate–severe airflow obstruction.

Bronchial Responsiveness

Although by definition, no COPD patients displays complete reversibility of airflow obstruction after bronchodilator inhalation (acute or chronic), some (about 12%) exhibit consistent and significant bronchodilator responsiveness (partial reversibility) to acute administration of an inhaled short-acting bronchodilator (salbutamol).[46] An increment in post-bronchodilator FEV_1 ≥12% from baseline with at least 200 mL absolute change defines this functional characteristic, which has been shown to be related to higher eosinophil count in induced sputum and elevated FeNO consistent with airway eosinophilic inflammation.[47] Therefore, the presence of significant bronchial responsiveness, suggesting a more likely eosinophilic airway inflammation[15] and also higher eosinophilic blood count,[48] may be considered a favorable predictor of ICS treatment.[49]

It must be recognized that a positive response to bronchodilators may be a mere consequence of FVC increase, with no change or even decrease in FEV_1/FVC ratio. This feature identifies COPD patients, so-called

volume responders, who are more frequently observed in GOLD stages 3 and 4.[50] In contrast, a similar significant FEV_1 increase after acute inhalation of short-acting bronchodilators may occur with an increase in FEV_1 /FVC ratio. This feature identifies COPD patients, so called flow responders, who are mostly found in GOLD stage 2, a milder stage of airflow obstruction where chronic bronchiolitis is the predominant disease underlying COPD.[46]

Prevention of Acute Exacerbations of COPD

Several studies in the last few years have focused on reduction of AECOPDs as a primary outcome of pharmacological treatments in COPD patients with a history of frequent COPD exacerbations.[7,8,35–41] About 35%–40% of COPD patients suffer from two or more AECOPDs or have a severe AECOPD leading to hospitalization each year.[51] Knowing independent risk factors for AECOPDs[51] and mainly the relevant negative role of frequent AECOPDs in the natural history of COPD,[52] effective prevention of these episodes of rapidly increased airway inflammation with a background of airway chronic inflammation has become a mandatory goal of treatment (pharmacological and non-pharmacological) in these COPD patients.[9,53,54]

It must be realized, however, that AECOPDs have different etiology, essentially infectious (viral, or bacterial, or both) and uninfectious.[9,33,55] Among those uninfectious, a number have sustained increased eosinophilic inflammation in the airways, as confirmed by sputum cytological analysis and reflected by peripheral blood eosinophilia, so-called eosinophilic AECOPDs.[33] Other AECOPDs, among those uninfectious and noneosinophilic, have several different causes that need to be identified from time to time.[9,55]

In each COPD patient who exhibits frequent exacerbations, a prevalent AECOPD phenotype seems involved,[56] which should be recognized and prevented accordingly, in order to reduce the overall AECOPD number, eg, by about 70%–80% and not about 20%–30%, as generally obtained in RCTs where every type of AECOPD is counted and the treatment to prevent them is the same. These stereotyped RCTs have also been done with ICSs, usually combined with long-acting or ultralong-acting bronchodilators.

Actually, is becoming clearly evident that ICSs are highly effective in preventing eosinophilic AECOPDs, which are the most prevalent phenotype in COPD patients suffering from chronic eosinophilic bronchiolitis, as already mentioned.[35–41] In contrast, ICSs could be useless or even noxious if chronically administered to prevent infectious AECOPDs or uninfectious and noneosinophilic AECOPDs if such phenotypes are mostly involved. In these cases, the risk of pneumonia may become unjustifiably elevated.[57] Therefore, in combination with bronchodilators, ICSs should be advised to prevent acute COPD exacerbations, essentially in COPD patients who have frequent eosinophilic AECOPDs, and not extensively in all COPD patients who have frequent AECOPDs.[58] Treatments other than ICSs have to be implemented in baseline pharmacological therapy to reduce the risk of noneosinophilic AECOPDs in frequent exacerbators.[9,53,59]

Asthma–COPD Overlap

Although asthma and fibrosing chronic bronchiolitis and/or pulmonary emphysema (asthma-COPD overlap [ACO]) rarely coexist in the same individual, this may occur and depicts an unfavorable clinical condition in terms of symptoms, acute exacerbations, quality of life, and use of rescue drugs.[60] In this context, the main difficulty remains the accurate identification of these patients, which is generally based on the presence of some anamnestic, clinical, functional, and possibly radiological features of both asthma and COPD,[61] namely subjects with a history of asthma and respiratory symptoms before age 40 years, presence of atopy and allergies, airflow obstruction not fully reversible, but with high responsiveness to bronchodilators, together with a relevant smoking history, and sometimes radiological aspects of pulmonary emphysema with reduced K_{CO}.[60,61] Despite the lack of specific interventional RCTs in patients with ACO, it is widely thought that ACO, especially when the underlying inflammatory endotype is eosinophilic, represents a strong indication for ICS treatment combined with long-acting bronchodilators,[62] in view of favorable effects on hospitalization and death as compared to LABAs alone, irrespective of lung-function impairment.[63]

Who

Based on the aforementioned observations, the profile of COPD patients who deserve ICSs emerges definitively, and has been previously outlined by the presence of predictors of a positive response.[49] Briefly, ICSs combined with bronchodilators are indicated as a disease-modifying drug to treat COPD patients: 1) who are suffering from chronic bronchiolitis as isolated or prevalent underlying disease (associated with mild–moderate centrilobular emphysema) (B); 2) who

in stable condition have an airway eosinophilic inflammation demonstrated by induced sputum and can be associated with persistent (and otherwise unexplained) blood eosinophilia (>-300–350 elements/μL) (E), and (if exacerbators) have prevalent eosinophilic exacerbations 3) who consistently show significant bronchial responsiveness after acute bronchodilators (ΔFEV_1 >12% from baseline with >200 mL increment), but with an increase in FEV_1/FVC ratio (so-called flow responders) (R); and 4) who are nonsmokers (ie, ex-smokers or never-smokers) (N). These COPD patients can be identified as BERN-positive (3 or 4 out of 4 criteria). In addition, the same is indicated for those COPD patients who have ACO.

In contrast, ICSs should do not be offered to COPD patients: 1) who suffer from panlobular emphysema or have developed confluent or advanced centrilobular emphysema as prevalent disease, respectively; 2) who do not have consistent eosinophilic inflammation in small airways or (if exacerbators) do not have eosinophilic exacerbations, but other causes of AECOPDs; 3) who do not respond to acute bronchodilators or show significant bronchial responsiveness, but with no change or decrease in FEV_1/FVC ratio (so-called volume-responders); and 4) who continue to smoke. These COPD patients can be identified as BERN-negative (3 or 4 out of 4 criteria). They should be treated only with one or two bronchodilators and specific measures to prevent AECOPDs if exacerbators, according to the prevalent cause of their AECOPDs (Figure 1).

When

In COPD patients who deserve ICSs because of the presence of the aforementioned characteristics ($BERN^+$), ICSs on top of one or two bronchodilators should be offered as soon as possible, independently of severity of symptoms, degree of airflow reduction, and presence of AECOPDs. In COPD patients who do not have these characteristics ($BERN^-$), ICSs should never be recommended.

Safety

The adverse effects of chronic ICS administration have been recognized for a long time and are a function of daily dose, being more common when higher dosage is assumed (ie, ≥1,000 μg fluticasone propionate equivalent per day). Although to a less extent than with systemic CSs, the risk of developing or worsening diabetes, cataracts, osteoporosis, adrenal insufficiency, active tuberculosis, skin bruises, and electrolyte imbalance is significantly increased in COPD patients consuming ICSs, especially at high doses.[49]

In contrast with asthmatics, however, COPD patients treated with ICSs have shown an increased risk of pneumonia compared with those who do not consume ICSs.[64] Although the risk of pneumonia seems mainly related to age, severity of airflow obstruction, history of AECOPDs, and comorbidities of COPD patients treated with ICSs[6,65] than ICS treatment per se, after

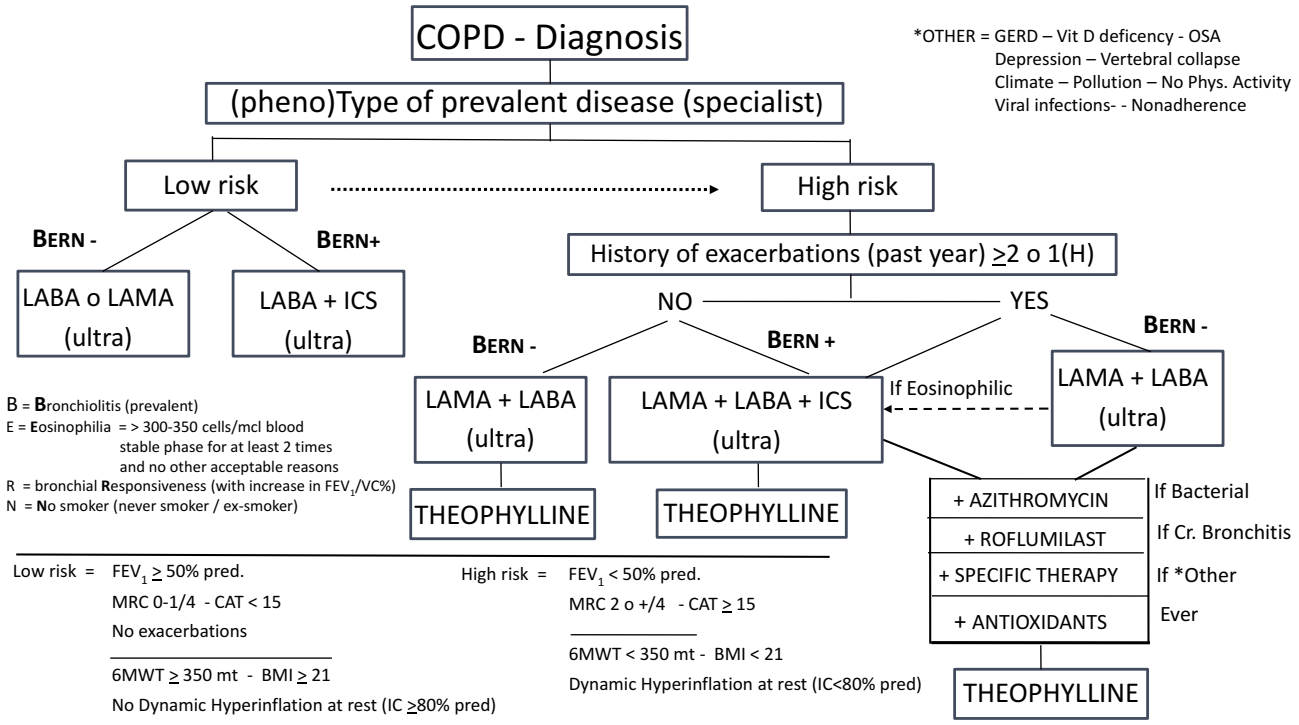

Figure 1 Targeted pharmacological treatment in COPD.

adjusting for these variables some significant residual risk persists that is a function of the duration and daily dose of ICSs consumed.[66] The size of the increased risk, the frequency of events, and the related excess mortality make pneumonia the most dangerous side effect in COPD patients treated with ICSs.[57]

Although the effect on AECOPD reduction has been much greater than the occurrence of pneumonia in previous RCTs, this does not justify the use of high doses of ICSs in treatment of COPD.[49] In fact, in studies where moderate doses of ICSs combined with bronchodilators have been used, the percentage of pneumonia was lower[67,68] or not different from the arm treated only with bronchodilators.[69,70] Notably, if ICSs are prescribed in COPD patients with high levels of blood eosinophilia to prevent AECOPDs (essentially eosinophilic), the risk of ICS-related pneumonia is reduced or even zero.[35] In summary, the risk of adverse effects of ICS treatment requires accurate selection of subgroups of COPD patients who warrant it and suggests the avoidance of high-dose ICSs in chronic therapy of these patients, with the only possible exception being patients with ACO.

Conclusion

Is clearly evident that the heterogeneity of patients affected by COPD should necessitate different treatment strategies. In this respect, the decision to adopt ICSs in combination with bronchodilators for chronic background therapy is crucial and has to be made at the beginning. The use of the simple BERN acronym (positive or negative) might be helpful in settling this choice. The usefulness of ICSs in the prevention of AECOPDs appears substantially limited to those eosinophilics that again belong to COPD patients who are BERN^{+}.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Global Initiative for Chronic Obstructive Lung Disease. Progetto Mondiale BPCO Strategia Globale Per La Diagnosi, Il Trattamento E La Prevenzione Della Broncopneumopatia Cronica Ostruttiva; Aggiornamento 2016 [World COPD Project Global Strategy For Diagnosis, Treatment And Prevention Of Chronic Obstructive Pulmonary Disease; Update 2016]. Available from: http://goldcopd.it/wp-content/uploads/materiali/2016/GOLD_workshop_report_2016.pdf. Accessed May 3, 2017. Italian.
2. Vestbo J, Sorensen T, Lange P, Brix A, Torre P, Viskum K. Long-term effect of inhaled budesonide in mild and moderate chronic obstructive pulmonary disease: a randomized controlled trial. *Lancet*. 1999;353:1819–1823. doi:10.1016/S0140-6736(98)10019-3
3. Pauwels RA, Lofdhal GG, Laitinen LA, et al. Long term treatment with inhaled budesonide in persons with mild chronic obstructive pulmonary disease who continue smoking. European Respiratory Society study on chronic obstructive pulmonary disease. *N Engl J Med*. 1999;340:1948–1953. doi:10.1056/NEJM199906243402503
4. The Lung Health Study Research Group. Effect of inhaled triamcinolone on the decline in pulmonary function in chronic obstructive pulmonary disease. *N Engl J Med*. 2000;343:1902–1909. doi:10.1056/NEJM200012283432601
5. Carlverley PMA, Pauwels RA, Vestbo J, et al. Combined salmeterol and fluticasone in the treatment of chronic obstructive pulmonary disease: a randomized controlled trial. *Lancet*. 2003;361:449–453. doi:10.1016/S0140-6736(03)12459-2
6. Calverley PMA, Anderson JA, Celli B, et al. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. *N Engl J Med*. 2007;356:775–789. doi:10.1056/NEJMoa063070
7. Kardos P, Wenker M, Glaab T, Volgelmeier C. Impact of salmeterol/fluticasone propionate versus salmeterol on exacerbation in severe chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2007;175:144–149. doi:10.1164/rccm.200602-244OC
8. Wedzicha JA, Calverley PMA, Seemungal TA, et al. The prevention of chronic obstructive pulmonary disease exacerbations by salmeterol/fluticasone propionate or tiotropium bromide. *Am J Respir Crit Care Med*. 2008;177:19–26. doi:10.1164/rccm.200707-973OC
9. Tantucci C, Pini L. COPD it is time to change! *Int J Chron Obstruct Pulmon Dis*. 2015;10:2451–2457. doi:10.2147/COPD.S87696
10. Brusselle G, Price D, Gruffydd-Jones K, et al. The inevitable drift to triple therapy in COPD: an analysis of prescribing pattern in the UK. *Int J Chron Obstruct Pulmon Dis*. 2015;10:2207–2217. doi:10.2147/COPD.S91694
11. Jen R, Rennard SI, Sin DD. Effects of inhaled corticosteroids on airway inflammation in chronic obstructive pulmonary disease: a systematic review and meta-analysis. *Int J Chron Obstruct Pulmon Dis*. 2012;7:587–595. doi:10.2147/COPD.S32765
12. Hogg JC, Chu FS, Utokaparch S, et al. The nature of small airway obstruction in chronic obstructive pulmonary disease. *N Engl J Med*. 2004;350:2645–2653. doi:10.1056/NEJMoa032158
13. Gan WQ, Man SF, Sin DD. Effects of inhaled corticosteroids on sputum cell counts in stable chronic obstructive pulmonary disease: a systematic review and a meta-analysis. *BMC Pulm Med*. 2005;5:3. doi:10.1186/1471-2466-5-3
14. Balzano G, Stefanelli F, Iorio C, et al. Eosinophilic inflammation in stable chronic obstructive pulmonary disease. Relationship with neutrophils and airway function. *Am J Respir Crit Care Med*. 1999;160:1486–1492. doi:10.1164/ajrccm.160.5.9810105
15. Perng DW, Huang HY, Chen HM, Lee YC, Perng RP. Characteristic of airway inflammation and bronchodilator reversibility in COPD: a potential guide to treatment. *Chest*. 2004;126:375–381. doi:10.1378/chest.126.2.375
16. Brightilng CE, McKenna S, Hargadon B, et al. Sputum eosinophilia and the short term response to inhaled mometasone in chronic obstructive pulmonary disease. *Thorax*. 2005;60:193–198. doi:10.1136/thx.2004.032516
17. Dummer JF, Epton MJ, Cowan JO, et al. Predicting corticosteroids response in chronic obstructive pulmonary disease using exhaled nitic oxide. *Am J Respir Crit Care Med*. 2009;180:846–852. doi:10.1164/rccm.200905-0685OC
18. Hoonhorst SJM, Ten Hacken NHT, Vonk JM, et al. Steroid resistance in COPD? Overlap and differential anti-inflammatory effects in smokers and ex-smokers. *PLoS One*. 2014;9(2):e87443. doi:10.1371/journal.pone.0087443
19. Barnes PJ, Adcock IM, Ito K. Histone acetylation and deacetylation: importance in inflammatory lung diseases. *Eur Respir J*. 2005;25:552–563. doi:10.1183/09031936.05.00117504

20. Kunz LIZ, Strebus J, Budulac SE, et al. Inhaled steroids modulate extracellular matrix composition in bronchial biopsies of COPD patients: a randomized, controlled trial. *PLoS One*. 2013;8(5): e63430. doi:10.1371/journal.pone.0063430
21. Glaab T, Taube C. Effects of inhaled corticosteroids in stable chronic obstructive pulmonary disease. *Pulm Pharmacol Ther*. 2011;24:15–22. doi:10.1016/j.pupt.2010.08.006
22. Lynch DA, Austin JH, Hogg JC, et al. CT-definable subtypes of chronic obstructive pulmonary disease: a statement of Fleischner Society. *Radiology*. 2015;277:192–205. doi:10.1148/radiol.2015141579
23. Bhatt SP, Soler X, Wang S, et al. Association between functional small airway disease and FEV_1 decline in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2016;194:178–184. doi:10.1164/rccm.201511-2219OC
24. Zhang X, Moilanen E, Kankaanranta H. Beclomethasone, budesonide and fluticasone propionate inhibit human neutrophil apoptosis. *Eur J Pharmacol*. 2001;431:365–371.
25. Lapperre TS, Snoeck-Stroband JB, Gosman MME, et al. Effect of fluticasone with and without salmeterol on pulmonary outcomes in chronic obstructive pulmonary disease. *Ann Intern Med*. 2009;151:517–527. doi:10.7326/0003-4819-151-8-200910200-00004
26. Snoeck-Stroband JB, Laperre TS, Sterk PJ, et al. Prediction of long-term benefits of inhaled steroids by phenotypic markers in moderate-to-severe COPD: a randomized controlled trial. *PLoS One*. 2015;10(12):e0143793. doi:10.1371/journal.pone.0143793
27. Nishimura M, Makita H, Nagai K, et al. Annual change in pulmonary function and clinical phenotype in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2012;185:44–52. doi:10.1164/rccm.201106-0992OC
28. Pizzichini E, Pizzichini MMM, Gibson P, et al. Sputum eosinophilia predicts benefit from prednisone in smokers with chronic obstructive bronchitis. *Am J Respir Crit Care Med*. 1998;158:1511–1517. doi:10.1164/ajrccm.158.5.9804028
29. Leigh R, Pizzichini MMM, Morris MM, Maltais F, Hargreave FE, Pizzichini E. Stabel COPD: predicting benefit from high-dose of inhaled corticosteroid treatment. *Eur Respir J*. 2006;27:964–971. doi:10.1183/09031936.06.00072105
30. Steiling K, van den Berge M, Hijazi K, et al. A dynamic bronchial airway gene expression signature of chronic obstructive pulmonary disease and lung function impairment. *Am J Respir Crit Care Med*. 2013;187:933–942. doi:10.1164/rccm.201208-1449OC
31. van den Berge M, Steiling K, Timens W, et al. Airway gene expression in COPD is dynamic with inhaled corticosteroid treatment and reflects biological pathways associated with disease activity. *Thorax*. 2014;69:14–23. doi:10.1136/thoraxjnl-2012-202878
32. Christenson SA, Steiling K, van den Berge M, et al. Asthma-COPD overlap. Clinical relevance of genomic signatures of type-2 inflammation in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2015;191.
33. Bafadhel M, McKenna S, Terry S, et al. Acute exacerbations of chronic obstructive pulmonary disease. Identification of biologic clusters and their biomarkers. *Am J Respir Crit Care Med*. 2011;184:662–671. doi:10.1164/rccm.201104-0597OC
34. Bafadhel M, McKenna S, Terry S, et al. Blood eosinophils to direct corticosteroid treatment of exacerbations of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2012;186:48–55. doi:10.1164/rccm.201108-1553OC
35. Pascoe S, Locantore N, Dransfield MT, Barnes NC, Pavord ID. Blood eosinophil count, exacerbations and response to the addition of inhaled fluticasone furoate to vilanterol in patients with chronic obstructive pulmonary disease: a secondary analysis of data from two parallel randomized controlled trials. *Lancet Resp Med*. 2015;435–442. doi:10.1016/S2213-2600(15)00106-X
36. Siddiqui SH, Guasconi A, Vestbo J, et al. Blood eosinophils: a biomarker of response to extrafine beclomethasone/formoterol in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2015;192:523–526. doi:10.1164/rccm.201502-0235LE
37. Wedzicha JA, Price D, Karen Mezzi K, Fogel R, Banerji D. Indacaterol plus Glypirronium compared with salmeterol/fluticasone on exacerbations and its correlation with baseline blood eosinophils: a pooled analysis of Lantern and Illuminate. *Eur Respir J*. 2015;46.
38. Ferguson GT, Rabe KF, Martinez FJ, et al. Triple therapy with budesonide/glycopyrrolate/formoterol fumarate with co-suspension delivery technology versus dual therapies in chronic obstructive pulmonary disease (KRONOS): a double-blind, parallel-group, multicentre, Phase 3 randomised controlled trial. *Lancet Resp Med*. 2018;6:747–758.
39. Watz H, Tetzlaff K, Wouters EF, et al. Blood eosinophil count and exacerbations in severe chronic obstructive pulmonary disease after withdrawal of inhaled c orticosteroids: a post-hoc analysis of the WISDOM trial. *Lancet Resp Med*. 2016;4:390–398. doi:10.1016/S2213-2600(16)00100-4
40. Bafadhel M, Peterson S, De Blas MA, et al. Predictors of exacerbation risk and response to budesonide in patients with chronic obstructive pulmonary disease: a post-hoc analysis of three randomised trials. *Lancet Respir Med*. 2018;6:117–126. doi:10.1016/S2213-2600(18)30006-7
41. Lipson DA, Barnhart F, Brealey N, et al. Once-daily single-inhaler triple versus dual therapy in patients with COPD. *New Engl J Med*. 2018;378:1671–1680. doi:10.1056/NEJMoa1713901
42. Suissa S, Dell'Aniello S, Ernst P. Comparative effectiveness of LABA-ICS versus LAMA as initial treatment in COPD targeted by blood eosinophils: a population-based cohort study. *Lancet Resp Med*. 2018;6:855–862. doi:10.1016/S2213-2600(18)30368-0
43. Brusselle GG, Bracke K, Lahousse L. Targeted therapy with inhaled corticosteroids in COPD according to blood eosinophil counts. *Lancet Resp Med*. 2015;3:416–417. doi:10.1016/S2213-2600(15)00145-9
44. Negewo NA, McDonald VM, Baines KJ, et al. Peripheral blood eosinophils: a surrogate marker for airway eosinophilia in stable COPD. *Int J Chron Obstruct Pulmon Dis*. 2016;11:1495.
45. Barnes NC, Sharma R, Lettis S, Calverley PMA. Blood eosinophils as a marker of response to inhaled corticosteroids in COPD. *Eur Respir J*. 2016;47:1374–1382. doi:10.1183/13993003.01370-2015
46. Albert P, Agusti A, Edwards L, et al. Bronchodilator responsiveness as a phenotypic characteristic of established chronic obstructive pulmonary disease. *Thorax*. 2012;67:701–708. doi:10.1136/thoraxjnl-2011-201458
47. Papi A, Romagnoli M, Baraldo S, et al. Partial reversibility of airflow limitation and increased exhaled NO and sputum eosinophilia in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2000;162:1773–1777. doi:10.1164/ajrccm.162.5.9910112
48. Sitkauskiene B, Sakalaukas R, Malakauskas K, Lotvall J. Reversibility to a beta-2-agonist in COPD: relationship to atopy and neutrophil activation. *Resp Med*. 2003;97:591–598. doi:10.1053/rmed.2003.1485
49. Ernst P, Saad N, Suissa S. Inhaled corticosteroids in COPD: the clinical evidence. *Eur Respir J*. 2015;45:525–537. doi:10.1183/09031936.00128914
50. Cerveri I, Pellegrino R, Dore R, et al. Mechanisms for isolated volume response to bronchodilator in patients with COPD. *J Appl Physiol*. 2000;88:1989–1995. doi:10.1152/jappl.2000.88.6.1989
51. Hurst JR, Vestbo J, Anzueto A, et al. Susceptibility to exacerbation in chronic obstructive pulmonary disease. *N Engl J Med*. 2010;363:1128–1138. doi:10.1056/NEJMoa0909883
52. Soler-Cataluna JJ, Martìnez-Garcìa MA, Romàn Sanchez P, Salcedo E, Navarro M, Ochando R. Severe acute exacerbations and mortality in patients with chronic obstructive pulmonary disease. *Thorax*. 2005;60:925–931. doi:10.1136/thx.2005.040527

53. Pavord ID, Jones PW, Burgel P-R, Rabe KF. Exacerbation of COPD. *Int J Chron Obstruct Pulmon Dis*. 2016;11:21–30. doi:10.2147/COPD.S85978
54. Wedzicha JA, Miravittles M, Hurst JR, et al. Management of COPD exacerbation: a European Respiratory Society/american Thoracic Society guideline. *Eur Respir J*. 2017;49:1600791. doi:10.1183/13993003.00791-2016
55. Zhou A, Zhou Z, Zhao Y, Chen P. The recent advances of phenotypes in acute exacerbations of COPD. *Int J Chron Obstruct Pulmon Dis*. 2017;12:1009–1018. doi:10.2147/COPD.S128604
56. Hurst JR. Exacerbation phenotyping in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2011;184:625–626. doi:10.1164/rccm.201106-1136ED
57. Suissa S, Patenaude V, Lapi F, et al. Inhaled corticosteroids in COPD and the risk of serious pneumonia. *Thorax*. 2013;68:1029–1036. doi:10.1136/thoraxjnl-2012-202872
58. Suissa S, Ernst P. Precision medicine urgency: the case of inhaled corticosteroids in COPD. *Chest*. 2017;152:227–231. doi:10.1016/j.chest.2017.05.020
59. Santos S, Marin A, Serra-Batlles J, et al. Treatment of patients with COPD and recurrent exacerbations: the role of infection and inflammation. *Int J Chron Obstruct Pulmon Dis*. 2016;11:515–525. doi:10.2147/COPD.S98333
60. Global Initiative for asthma (GINA). Global strategy for asthma management and prevention; 2018. Available from: http://www.ginasthma.org/guideline-report-2018.htlm. Accessed March 26, 2020.
61. Gibson PG, Simpson JL. The overlap syndrome of asthma and COPD: what are its feature and how important is it? *Thorax*. 2009;64:728–735. doi:10.1136/thx.2008.108027
62. Kitaguchi YK, Komatsu Y, Fujimoto K, Hanaoka M, Kubo K. Sputum eosinophilia can predict responsiveness to inhaled corticosteroid treatment in patients with overlap syndrome of COPD and asthma. *Int J Chron Obstruct Pulmon Dis*. 2012;7:283–289. doi:10.2147/COPD.S30651
63. Gershon AS, Campitelli MA, Croxford R, et al. Combination of long-acting β-agonists and inhaled corticosteroids compared with long-acting β-agonists alone in older adults with chronic obstructive pulmonary disease. *JAMA*. 2014;312:1114–1121. doi:10.1001/jama.2014.11432
64. Almirall J, Bolibar I, Serra-Prta M, et al. New evidence of risk factors for community-acquired pneumonia: a population-based study. *Eur Respir J*. 2008;31:1274–1284. doi:10.1183/09031936.00095807
65. Crim C, Calvereley PM, Anderson JA, et al. Pneumonia risk in COPD patients receiving inhaled corticosteroids alone or in combination: TORCH study results. *Eur Respir J*. 2009;34:641–647. doi:10.1183/09031936.00193908
66. Kew KM, Seniukovich A. Inhaled steroids and risk of pneumonia for chronic obstructive pulmonary disease. *Cochrane Database Sys Rev*. 2014;CD010115.
67. Ferguson GT, Anzueto A, Fei R, Emmet A, Knobil K, Kalberg C. Effect of fluticasone propionate/salmeterol (250/50 microg) or salmeterol (50 microg) on COPD exacerbations. *Respir Med*. 2008;102:1099–1108. doi:10.1016/j.rmed.2008.04.019
68. Anzueto A, Ferguson GT, Feldman G, et al. Effect of fluticasone propionate/salmeterol (250/50 microg) on COPD exacerbations and impact on patient outcomes. *COPD*. 2009;6:320–329. doi:10.1080/15412550903140881
69. Vestbo J, Papi A, Corradi M, et al. Single inhaler extrafine triple therapy versus long-acting muscarinic antagonist therapy for chronic obstructive pulmonary disease (TRINITY): a double-blind parallel group, randomized controlled trial. *Lancet*. 2017;389:1919–1929. doi:10.1016/S0140-6736(17)30188-5
70. Papi A, Vestbo J, Fabbri L, et al. Extrafine inhaled triple therapy versus dual bronchodilator therapy in chronic obstructive pulmonary disease (TRIBUTE): a double-blind parallel group, randomized controlled trial. *Lancet*. 2018;391:1076–1084. doi:10.1016/S0140-6736(18)30206-X