Chronic Obstructive Pulmonary Diseases:
Journal of the COPD Foundation

Journal Club

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Abbreviations: inhaled corticosteroid, **ICS**; long acting β_2-agonist, **LABA**; Global initiative for chronic Obstructive Pulmonary Disease, **GOLD**; long-acting muscarinic antagonists, **LAMA**; Withdrawal of Inhaled Steroids during Optimized Bronchodilator Management, **WISDOM**; modified Medical Research Council, **mMRC**; forced expiratory volume in 1 second, **FEV_1**; diabetes, **DM**; Study to Understand Mortality and Morbidity in COPD, **SUMMIT**; Investigating New Standards for Prophylaxis in Reducing Exacerbations trial, **INSPIRE**;

Funding Support: n/a
Date of Acceptance: December 2, 2014
Citation: Balkissoon R. Journal club. *J COPD F*. 2015;2(1): 85-90. doi: http://dx.doi.org/10.12356/jcopdf.2.1.2014.0162

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Keywords:

COPD; inhaled corticosteroids; long-acting ß$_2$-agonists; long-acting muscarinic antagonists; exacerbations; pneumonia; mortality

Abstract 1

Withdrawal of inhaled glucocortcoids and exacerbations of COPD

Magnussen H, Disse B, Rodriguez-Roisin R, et al and the WISDOM Investigators. *N Engl J Med*. 2014;371(14):1285-1294.

Background: Treatment with inhaled glucocorticoids in combination with long-acting bronchodilators is recommended in patients with frequent exacerbations of severe chronic obstructive pulmonary disease (COPD). However, the benefit of inhaled glucocorticoids in addition to 2 long-acting bronchodilators has not been fully explored.

Methods: In this 12-month, double-blind, parallel-group study, 2485 patients with a history of exacerbation of COPD received triple therapy consisting of tiotropium (at a dose of 18 µg once daily), salmeterol (50 µg twice daily), and the inhaled glucocorticoid fluticasone propionate (500 µg twice daily) during a 6-week run-in period. Patients were then randomly assigned to continued triple therapy or withdrawal of fluticasone in 3 steps over a 12-week period. The primary end point was the time to the first moderate or severe COPD exacerbation. Spirometric findings, health status, and dyspnea were also monitored.

Results: As compared with continued inhaled glucocorticoid use, glucocorticoid withdrawal met the prespecified noninferiority criterion with respect to the first moderate or severe COPD exacerbation (hazard ratio, 1.06; 95% confidence interval, 0.94 to 1.19). At week 18, when glucocorticoid withdrawal was complete, the adjusted mean reduction from baseline in the trough forced expiratory volume in 1 second was 38 ml greater in the glucocorticoid-withdrawal group than in the glucocorticoid-continuation group (P<0.001); a similar between-group difference (43 ml) was seen at week 52 (P=0.001). No change in dyspnea and minor changes in health status occurred in the glucocorticoid-withdrawal group.

Conclusions: In patients with severe COPD receiving tiotropium plus salmeterol, the risk of moderate or severe exacerbations was similar among those who discontinued inhaled glucocorticoids and those who continued glucocorticoid therapy. However, there was a greater decrease in lung function during the final step of glucocorticoid withdrawal.

Comments

Initially the inhaled corticosteroid (ICS)/long acting β_2-agonist (LABA) fluticasone propionate/salmeterol combination studies demonstrated improvements in lung function in patients with COPD[1] that led to

its approval with the indication for improvement in symptoms and lung function of COPD patients with chronic bronchitis and emphysema. Subsequent studies demonstrated a significant reduction in exacerbations for this formulation.[2] The Global initiative for chronic Obstructive Lung Disease (GOLD) guidelines recommend including the ICS/LABA class for individuals that have low lung function (less than 50% predicted) and/or frequent exacerbations (2 or more per year or 1 hospitalization). Nonetheless, in the past few years there has been a re-evaluation of the role of ICSs in the treatment of COPD given that many patients report side effects of thrush and hoarseness and/or have comorbidities that can be potentiated by an ICS such as cataracts, diabetes, osteopenia, and recurrent pneumonia. Hence, it is reasonable to study whether individuals that have been stabilized on triple therapy with ICS/LABA/long-acting muscarinic antagonists (LAMA) can be "stepped down" to LABA/LAMA alone and maintain a similar level of clinical stability. With that in mind, the Withdrawal of Inhaled Steroids during Optimized Bronchodilator Management (WISDOM) trial set out to examine whether ICS (fluticasone propriaate) withdrawal would have an impact on patients that remained on a LABA (salmeterol) and a LAMA (tiotropium). This was a large and ambitious study (2485 participants) and assists in shedding light on the appropriate placement of LABA/LAMA therapy in COPD but it is challenging to decide how the findings from this study should be translated into clinical practice.

Patient inclusion criteria were that patients had to have had at least 1 exacerbation in the past 12 months, indeed 1537 patients had 1 exacerbation and 903 had 2 or more exacerbations in the previous 12 months. The modified Medical Research Council (mMRC) dyspnea score was 1.8 on average prior to study entry. The forced expiratory in 1 second (FEV_1) had to be less than 50% of predicted. Prior to entering the study 39% were on triple therapy, 69.9% on ICS, 64.6% on LABA and 46% on LAMA. In terms of comorbidity 28.2% had cardiac disorders, 45.8% had vascular disorders. They were not allowed to be on oral steroids during the trial or leading up to the trial. Salbutamol (albuterol) was allowed as a rescue inhaler. The study group was 82.5% men, the mean FEV_1 post bronchodilator 32.8% of predicted with about 60% with an FEV_1 between 30%-50% and approximately 40% with an FEV_1 less than 30%. Baseline FEV_1 assessed after receiving triple therapy including fluticasone 500µg bid daily for 6 weeks was approximately 34%.

Their primary endpoint was time to the first moderate or severe exacerbation during the 12 month period (although participants in the withdrawal arm were actually only off of fluticasone for the last 9 months of the study). Moderate exacerbations were those with an increase in at least 1 symptom for 3 days leading to treatment with systemic steroids and/or antibiotics. Severe exacerbations were those requiring hospitalization in an urgent care unit. Exacerbations were determined on the basis of review of patient questionnaires during the visit dates and daily symptom diaries. The authors concluded that in patients with severe but stable COPD the stepwise withdrawal of corticosteroids was non-inferior to the continuation of such therapy with respect to the risk of moderate or severe exacerbations as assessed by time to first moderate or severe exacerbation.

If the primary outcome being studied concerns exacerbations then it would seem optimal to study the group for whom there is an exacerbation indication. Considering that the majority of patients in this study would not meet exacerbation criteria for steroid use according to current GOLD guidelines (2 or more in past 12 months or 1 hospitalization) then it is perhaps not surprising, particularly in a non-inferiority study, that there was no statistical difference with regard to time to first exacerbation. Perhaps this reflects the fact that this study was conceived before the most recent GOLD recommendations but the basis for the previous recommendations for use of ICS in patients with FEV_1 less than 50% of predicted was predicated on the evidence that that group was more likely to have 2 or more exacerbations per year. It may have been useful to do a subgroup analysis of those that met the current criteria of 2 exacerbations per year or 1 hospitalization.

Interestingly, there was a modest but statistically significant difference in FEV_1 at week 18 that had further increased by end of the trial that would have been in favor of continued ICS use. The irony is that for over 60% of this cohort reduced lung function would have been the indication for ICS use.

Further, the use of time to first exacerbation (as opposed to exacerbation frequency) as the primary outcome, and the fact that the withdrawal group was only off for 9 months also presents issues with regard to interpreting the data. Exacerbation frequency has a seasonal variation (centers were based in Europe,

Asia, Australia, South America and North Africa) and can be related to influenza and other viral epidemics. Comparisons should follow the participants over exactly the same periods of time and studies covering periods of 12 months help to overcome this issue and in this instance the 9 month period during which participants were entirely off steroids may be particularly liable to time/place confounding and does not take into account the interval from last exacerbation to trial entry.

Hence the practical clinical implications of this study would seem to be that patients with mild to moderate symptoms (mMRC dyspnea score <2) but low lung function (FEV_1 < 50% predicted) and infrequent exacerbations (less than 2) could be considered for step down therapy to long-acting bronchodilators alone after a trial of triple therapy. They may not experience any worsening in their exacerbation rate but may see a loss of lung function. Many in this cohort would have fallen into Group C of the current GOLD classification (mMRC ≤2, FEV_1< 50%) and would have not normally been considered for triple therapy treatment. Further the rationale for the withdrawal protocol (dropping from 1000 to 500 to 200 µg daily every 6 weeks) is unclear and potentially burdensome and wasteful to the patients as this would require the use of 1.5 inhalers of each dose formulation if used as a combination inhaler with salmeterol or some odd combination of ICS inhaler alone and LABA inhaler alone. There are also certain countries where there is only an indication for use of the 250 µg bid dose equivalent of fluticasone in combination with salmeterol for treatment of COPD. It may be the case that those patients with low lung function (FEV_1 < 50%) but less than 2 moderate exacerbations per year may do well with initiation of LABA/LAMA without need for ICS step-down but this study design does not allow us to address that question directly. With one combination LABA/LAMA currently available and another likely to become available in the near future, it would be helpful to have studies that provide guidance as to their appropriate placement and use. While we may have gained some insight into the theoretical feasibility of step down therapy from this study, further studies will be useful to gain greater clarity as to the practical clinical application of step down therapy and placement of LABA/LAMA combination drugs in treatment of COPD patients.

Abstract 2

Quantifying the real life risk profile of inhaled corticosteroids in COPD by record linkage analysis

Flynn RW, MacDonald TM, Hapca A, MacKenzie IS, Schembri S. *Respir Res*. 2014;15(1):141.

Background: Inhaled corticosteroids (ICS), especially when prescribed in combination with long-acting ß$_2$-agonists have been shown to improve COPD outcomes. Although there is consistent evidence linking ICS with adverse effects such as pneumonia, the complete risk profile is unclear with conflicting evidence on any association between ICS and the incidence or worsening of existing diabetes, cataracts and fractures. We investigated this using record linkage in a Dundee COPD population.

Methods: A record linkage study linking COPD and diabetes datasets with prescription, hospitalization and mortality data via a unique Community Health Index number. A Cox regression model was used to determine the association between ICS use and new diabetes or worsening of existing diabetes and hospitalizations for pneumonia, fractures or cataracts after adjusting for potential confounders. A time dependent analysis of exposure comparing time on versus off ICS was used to take into account patients changing their exposure status during follow-up and to prevent immortal time bias.

Results: 4305 individuals (3243 exposed to ICS, total of 17,229 person-years of exposure and 1062 non-exposed, with a follow-up of 4508 patient-years) were eligible for the study. There were 239 cases of new diabetes (DM) and 265 cases of worsening DM, 550 admissions for pneumonia, 288 hospitalizations for fracture and 505 cataract-related admissions. The hazard ratios for the association between cumulative ICS and outcomes were 0.70 (0.43-1.12), 0.57 (0.24-1.37), 1.38 (1.09-1.74), 1.08 (0.73-1.59) and 1.42 (1.07-1.88) after multivariate analysis respectively.

Conclusion: The use of ICS in our cohort was not associated with new onset of diabetes, worsening of existing diabetes or fracture hospitalization. There was however, an association with increased cataracts and pneumonia hospitalizations.

Comments

COPD patients have multiple comorbidities and risk. Some are directly related to their history of cigarette smoking such as cardiovascular disease but some have been attributed or at least associated with inhaled corticosteroid use. The results of this trial provide data with regard to consequences of long term use of inhaled corticosteroids. This is a fairly large cohort analysis and demonstrates that indeed there are increased hospitalizations related to pneumonia and an increased risk of cataracts. They did not factor in oral steroid use when it came to the analysis for cataracts. We also do not have information on the breakdown as far as severity of disease and there is no analysis provided with regard to the type of inhaled corticosteroids used. Nonetheless, it indeed affirms that the pneumonia and cataract risk is not insignificant but also informs concerns about the risks of diabetes and significant osteopenia-related fractures.

Abstract 3
Incident pneumonia and mortality in COPD patients - A double-effect of inhaled corticosteroids?

Festic E, Scanlon PD. *Am J Respir Crit Care Med*. 2014 Nov 19; [Epub ahead of print]

Inhaled corticosteroids are commonly prescribed for patients with severe COPD. Although their use improves quality of life and reduces exacerbations, it is associated with increased risk of pneumonia. Curiously, their use has not been associated with increased risk of pneumonia-related or overall mortality. We review pertinent literature to further explore the effects of inhaled corticosteroids on incident pneumonia and mortality in patients with COPD. The association of use of inhaled corticosteroids and incident pneumonia is substantial, and has been present in the majority of the studies on the topic. This includes both randomized controlled trials as well as observational studies. However, all of the studies have substantial risk of bias. Most randomized trials are limited by lack of systematic ascertainment of pneumonia; they depended on adverse event reporting. Many observational studies included proper radiographic assessment of pneumonia, but they are limited by their retrospective, observational design. The unadjusted higher risk of pneumonia is associated with longer duration of use, more potent ICS compounds, and higher doses. That implies a dose-effect relationship. Unlike pneumonia, mortality is a precise outcome. Despite the robust association of inhaled corticosteroid use with increased risk of pneumonia, all studies find either no difference or a reduction in pulmonary-related and overall mortality associated with the use of inhaled corticosteroids. These observations suggest a double-effect of inhaled corticosteroids, i.e. an adverse effect plus an unexplained mitigating effect.

Comments

This comprehensive literature review provides more insight into the relationship between pneumonia and inhaled corticosteroid use. While there is no dispute that there is an association between pneumonia and ICS use, there consistently remains no signal of an increase in pneumonia-related mortality or all cause mortality. The exact nature of the relationship between pneumonia and ICS use remains unclear and is likely multifactorial including reductions in local immunity and suppression of the release of cytokines that elicit local and constitutional symptoms such as cough, sputum production, fever and general malaise that normally lead to earlier recognition by the patient that they are getting sick. It is also important, as this study points out, that this risk does seem to be associated with higher doses of ICS. The Investigating New Standards for Prophylaxis in Reducing Exacerbations (INSPIRE) trial[2] showed that over half of all the pneumonias in the ICS arm were consequences of unresolved exacerbations. The authors offer that despite the increased incidence of pneumonia the fact that there is no increase in pneumonia- related mortality or in overall mortality suggests a potential *double effect* of inhaled corticosteroids. They suggest that ICS may reduce the severity of pneumonia episodes and/or reduce overall mortality. Current ongoing studies such as the Study to Understand Mortality and Morbidity in COPD (SUMMIT) trial[3] that examines the potential reduction in cardiovascular mortality related to ICS use may further help to explain these observations.

Abstract 4
Comparing the effectiveness of small-particle versus large-particle inhaled corticosteroid in COPD

Postma DS, Roche N, Colice G, et al. *Int J Chron Obstruct Pulmon Dis*. 2014;9:1163-1186.

Purpose: Small airway changes and dysfunction contribute importantly to airway obstruction in chronic obstructive pulmonary disease (COPD), which is currently treated with inhaled corticosteroids (ICS) and long-acting bronchodilators at Global initiative for Obstructive Lung Disease (GOLD) grades 2-4. This retrospective matched cohort analysis compared effectiveness of a representative small-particle ICS (extrafine beclomethasone) and larger-particle ICS (fluticasone) in primary care patients with COPD.

Patients and Methods: Smokers and ex-smokers with COPD ≥40 years old initiating or stepping-up their dose of extra fine beclomethasone or fluticasone were matched 1:1 for demographic characteristics, index prescription year, concomitant therapies, and disease severity during 1 baseline year. During 2 subsequent years, we evaluated treatment change and COPD exacerbations, defined as emergency care/hospitalization for COPD, acute oral corticosteroids, or antibiotics for lower respiratory tract infection.

Results: Mean patient age was 67 years, 57%-60% being male. For both initiation (n=334:334) and step-up (n=189:189) patients, exacerbation rates were comparable between extra fine beclomethasone and fluticasone cohorts during the 2-year outcome period. Odds of treatment stability (no exacerbation or treatment change) were significantly greater for patients initiating extra fine beclomethasone compared with fluticasone (adjusted odds ratio 2.50; 95% confidence interval, 1.32-4.73). Median ICS dose exposure during 2 outcome years was significantly lower (P<0.001) for extra fine beclomethasone than fluticasone cohorts (315 µg/day versus 436 µg/day for initiation, 438 µg/day versus 534 µg/day for step-up patients).

Conclusion: We observed that small-particle ICS at significantly lower doses had comparable effects on exacerbation rates as larger-particle ICS at higher doses, whereas initiation of small-particle ICS was associated with better odds of treatment stability during 2-years' follow-up.

Comments

Studies by Jim Hogg[4] and others have outlined the significant involvement of the small airways in the pathogenesis of COPD. This is a retrospective observational study of 2 large primary care databases in the United Kingdom but addresses an important question as to whether small particle ICS may have greater or equal efficacy than large particle ICS with regard to reduction of exacerbations in patients with COPD but at lower doses given some of the safety concerns. Those who were new starts on ultra fine beclamethasone showed evidence of greater success, i.e. exacerbation free for the 2 years of the study compared to fluticasone. The fact that the study showed evidence of similar reductions in exacerbation rates for both beclomethasone and fluticasone and showed greater treatment stability with a lower dose of extra fine beclomethasone suggests that targeting smaller airways with small particle ICS is a potentially valuable treatment option in combination with a LABA and/or LAMA. The retrospective nature of this study, the fact that patients who were given the co-diagnosis of asthma after the age of 40 could be included in the analysis, and the fact that there was no selection of patients that were known to be frequent exacerbators as an inclusion criteria outline the rationale for a prospective randomized control trial.

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