Chronic Obstructive Pulmonary Diseases:
Journal of the COPD Foundation

Journal Club

The Journal Club: COPD Exacerbations

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Abbreviations: chronic obstructive pulmonary disease, **COPD**; Global initiative for chronic Obstructive Lung Disease, **GOLD**; inhaled corticosteroid, **ICS**; long- acting muscarinic antagonist, **LAMA**; long-acting beta-agonist, **LABA**

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Introduction

In this issue, I review articles that provide further insights into the pathogenesis and/or management of chronic obstructive pulmonary disease (COPD) exacerbations. Exacerbations remain a significant source of cost, morbidity and progression of disease. The current Global initiative for chronic Obstructive Lung Disease (GOLD) guidelines[1] focus on symptoms and exacerbations as the major factors to consider in treatment escalation. In the earlier editions of COPD recommendations and guidelines, inhaled corticosteroids (ICSs) have played a central role in dealing with acute exacerbations. The most recent iteration of the (GOLD) guidelines suggests that long-acting muscarinic antagonists (LAMAs) are first line therapy for patients with a history of 2 or more exacerbations in the previous 12 months. If these fail then a combination with a long-acting beta-agonist (LABA) is recommended. The recommendation to try LAMAs or a LABA/LAMA combination before an ICS/LABA combination for treatment of exacerbations appears to be related in large part to evidence that there may be an increased risk of pneumonia with use of inhaled corticosteroids for at least some COPD patients. In the last Journal Club, I highlighted that there remains an ongoing debate with regard to whether there is a subset of patients for whom ICS/LABAs may be a preferred first choice. The first paper presented in this Journal Club, the TRINITY Trial, compares a new triple combination ICS/LABA/LAMAs versus the use of LAMA alone for prevention of COPD exacerbations. The second paper reviewed is the most recent American Thoracic Society/European Respiratory Society guidelines for treatment of acute exacerbations. It provides a thorough review of the literature regarding the evidence for some of the most common practices in the treatment of acute exacerbations, from use of oral steroids and antibiotics to in-home management with non-invasive ventilation. Finally, I have included an interesting paper that examines the potential role of secretory IgA deficiency in select small airways as a potential pathogenic mechanism for persistent small airway inflammation and reinfection in patients with frequent COPD exacerbations.

Abstract 1
Single Inhaler Extrafine Triple Therapy Versus Long-Acting Muscarinic Antagonist Therapy for Chronic Obstructive Pulmonary Disease (TRINITY): A Double-Blind, Parallel Group, Randomised Controlled Trial

Vestbo J, Papi A, Corradi M, et al. *Lancet*. 2017;389(10082):1919-1929.

BACKGROUND:
Limited data are available for the efficacy of triple therapy with two long-acting bronchodilators and an inhaled corticosteroid in chronic obstructive pulmonary disease (COPD). We compared treatment with extrafine beclometasone dipropionate, formoterol fumarate, and glycopyrronium bromide (BDP/FF/GB; fixed triple) with tiotropium, and BDP/FF plus tiotropium (open triple).

METHODS:
For this double-blind, parallel-group, randomised, controlled trial, eligible patients had COPD, post-bronchodilator forced expiratory volume in 1 s (FEV_1) of less than 50%, at least one moderate-to-severe COPD exacerbation in the previous 12 months, and a COPD Assessment Test total score of at least 10. After a 2-week run-in period receiving one inhalation per day via single-dose dry-powder inhaler of open-label 18 µg tiotropium, patients were randomised (2:2:1) using a interactive response technology system to 52 weeks treatment with tiotropium, fixed triple, or open triple. Randomisation was stratified by country and severity of airflow limitation. The primary endpoint was moderate-to-severe COPD exacerbation rate. The key secondary endpoint was change from baseline in pre-dose FEV_1 at week 52. The trial is registered with ClinicalTrials.gov, number NCT01911364.

FINDINGS:
Between Jan 21, 2014, and March 18, 2016, 2691 patients received fixed triple (n=1078), tiotropium (n=1075), or open triple (n=538). Moderate-to-severe exacerbation rates were 0.46 (95% CI 0.41-0.51) for fixed triple, 0.57 (0.52-0.63) for tiotropium, and 0.45 (0.39-0.52) for open triple; fixed triple was superior to tiotropium (rate ratio 0.80 [95% CI 0.69-0.92]; p=0.0025). For week 52 pre-dose FEV_1, fixed triple was superior to tiotropium (mean difference 0.061 L [0.037 to 0.086]; p<0.0001) and non-inferior to open triple (-0.003L [-0.033 to 0.027]; p=0.85). Adverse events were reported by 594 (55%) patients with fixed triple, 622 (58%) with tiotropium, and 309 (58%) with open triple.

INTERPRETATION:
In our TRINITY study, treatment with extra fine fixed triple therapy had clinical benefits compared with tiotropium in patients with symptomatic COPD, FEV_1 of less than 50%, and a history of exacerbations.

FUNDING:
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Comments

The most recent iteration of the GOLD guidelines suggests that patients with a history of 2 or more exacerbations in the previous 12 months may be able to reduce the rate of exacerbations with use of a LAMA alone at least as well as an ICS/LABA combination without the increased risk of pneumonia.[1] A previous study, TRILOGY,[2] demonstrated that the triple therapy used in the current study significantly reduced COPD exacerbations compared to just the ICS/LABA components. Like other studies that have examined this question, participants only had to have 1 exacerbation in the previous 12 months. This is likely the major explanation for the relatively low number of events in this study. For the current study, it is worth noting that patients with a history of asthma or allergic rhinitis were excluded but a history of pneumonia was not an exclusion criteria. Participants were excluded if they had been on triple therapy. The average exacerbation rate for the previous 12 months was only 1.2 to 1.3. Before entry into the trial, approximately 75% of patients were on ICS/LABA combinations, 12% to 14% were on LABA/LAMA combinations and only about 10% had been on LAMA monotherapy. Almost 50% of patients were current smokers. The 3 treatment groups had similar average blood eosinophil counts (200 eos/microliter). Interestingly, the greatest response noted was for participants with at least 2% eosinophils (or

200 eos /μl) with a 30 % reduction in exacerbations in the triple therapy group compared to the tiotropium group. Serious adverse events of pneumonia were noted in 21(2%) of patients on fixed triple therapy, 9(2%) on open triple therapy versus 14(1%) on tiotropium. The study was not powered to statistically analyze for differences in rates of pneumonia.

The authors' conclusion that "...This consistent improvement in different disease domains suggests that stepping up a patient from long-acting muscarinic antagonist to triple therapy will have a clinically meaningful impact," would seem to imply that even patients with 1 exacerbation in the past year are likely to benefit from triple therapy compared to LAMA alone. It is important to note however that these patients are not "maintenance therapy naïve" at the onset of the study. The majority of patients across all 3 treatment-arms were on ICS/LABA (75%) versus 10% (LAMA) prior to trial onset. By study design it has already preselected a group that have failed these maintenance therapies and in fact, the majority of participants had experienced at least 1 exacerbation despite being on an ICS/LABA combination prior to onset of the trial. There was no difference between the single triple and the ICS/LABA + LAMA group. Hence, this study supports the escalation to triple therapy for those who have ongoing exacerbations despite having been on ICS/LABA, LAMA alone or LABA/LAMA, (as the GOLD guidelines recommend). For patients that have not been on previous maintenance therapy, it is still appropriate to try LAMA, LABA/LAMA or ICS/LABA first to see if these reduce exacerbations before immediately stepping up to triple therapy.

Abstract 2
Management of COPD Exacerbations: A European Respiratory Society/American Thoracic Society Guideline

Wedzicha JA, Miravitlles M, Hurst JR, et al. *Eur Respir J*. 2017;49(3).

This document provides clinical recommendations for treatment of chronic obstructive pulmonary disease (COPD) exacerbations. Comprehensive evidence syntheses, including meta-analyses, were performed to summarise all available evidence relevant to the Task Force's questions. The evidence was appraised using the Grading of Recommendations, Assessment, Development and Evaluation approach and the results were summarised in evidence profiles. The evidence syntheses were discussed and recommendations formulated by a multidisciplinary Task Force of COPD experts. After considering the balance of desirable and undesirable consequences, quality of evidence, feasibility, and acceptability of various interventions, the Task Force made: 1) a strong recommendation for noninvasive mechanical ventilation of patients with acute or acute-on-chronic respiratory failure; 2) conditional recommendations for oral corticosteroids in outpatients, oral rather than intravenous corticosteroids in hospitalised patients, antibiotic therapy, home-based management, and the initiation of pulmonary rehabilitation within 3 weeks after hospital discharge; and 3) a conditional recommendation against the initiation of pulmonary rehabilitation during hospitalization. The Task Force provided recommendations related to corticosteroid therapy, antibiotic therapy, noninvasive mechanical ventilation, home-based management, and early pulmonary rehabilitation in patients having a COPD exacerbation. These recommendations should be reconsidered as new evidence becomes available.

Comments

This guideline is a state of the art summary of the current level of evidence for many common practices in the management of acute exacerbations of COPD. Not only does it provide an excellent review of the literature and level of evidence for the recommendations but also

compares these recommendations with those of other societies and organizations. It is rather sobering to look at the level of evidence to support the majority of the recommendations covered in this Guideline. While some of the recommendations such as antibiotic use and oral steroids have modest economic and clinical impact, other recommendations such as use of noninvasive ventilation and home-based management of acute exacerbations have significant economic and quality of care implications that warrant further rigorous study.

Abstract 3
Secretory IgA Deficiency in Individual Small Airways is Associated with Persistent Inflammation and Remodeling

Polosukhin VV, Richmond BW, Du RH. *Am J Respir Crit Care Med*. 2017;195(8):1010-1021.

RATIONALE:
Maintenance of a surface immune barrier is important for homeostasis in organs with mucosal surfaces that interface with the external environment; however, the role of the mucosal immune system in chronic lung diseases is incompletely understood.

OBJECTIVES:
We examined the relationship between secretory IgA (SIgA) on the mucosal surface of small airways and parameters of inflammation and airway wall remodeling in chronic obstructive pulmonary disease (COPD).

METHODS:
We studied 1,104 small airways (<2 mm in diameter) from 50 former smokers with COPD and 39 control subjects. Small airways were identified on serial tissue sections and examined for epithelial morphology, SIgA, bacterial DNA, nuclear factor-κB activation, neutrophil and macrophage infiltration, and airway wall thickness.

MEASUREMENTS AND MAIN RESULTS:
Morphometric evaluation of small airways revealed increased mean airway wall thickness and inflammatory cell counts in lungs from patients with COPD compared with control subjects, whereas SIgA level on the mucosal surface was decreased. However, when small airways were classified as SIgA intact or SIgA deficient, we found that pathologic changes were localized almost exclusively to SIgA-deficient airways, regardless of study group. SIgA-deficient airways were characterized by (1) abnormal epithelial morphology, (2) invasion of bacteria across the apical epithelial barrier, (3) nuclear factor-κB activation, (4) accumulation of macrophages and neutrophils, and (5) fibrotic remodeling of the airway wall.

CONCLUSIONS:
Our findings support the concept that localized, acquired SIgA deficiency in individual small airways of patients with COPD allows colonizing bacteria to cross the epithelial barrier and drive persistent inflammation and airway wall remodeling, even after smoking cessation.

KEYWORDS:
NF-κB; chronic obstructive pulmonary disease; neutrophils; secretory IgA; small airways

Comments

The seminal work of Jim Hogg and his colleagues[3] identified that the small airways are a major target for the injury incurred by smokers susceptible to the effects of cigarette smoke yet the exact pathophysiology is incompletely understood. This paper provides insights into the mechanisms that may render some individuals more susceptible to the airway remodeling and chronic persistent inflammation that occurs in COPD patients even after they have stopped smoking. All participants had to be former smokers to eliminate any acute influences on ongoing cigarette smoke. Control samples were from lungs, not used for lung transplant, from 24 lifelong nonsmoker donors without lung disease and 11 former smokers without COPD. There were 4 former smokers without COPD who had lungs resected with solitary tumors. COPD lungs were obtained from transplanted patients' explanted lungs. Control participants who were former smokers had about a 37-pack year history, whereas the COPD groups ranged in pack years from 46.3 to 60.6 pack years.

Interestingly, the patients with stage IV COPD had the lowest pack year history (46.3) of all the COPD patients. The former smokers who did not have COPD

had a slightly higher range for secretory IgA deficient airways than the lifelong non-smoker controls but they were indeed substantially lower than the patients with COPD. Even more compelling was the evidence that patients with more severe disease had substantially higher numbers of secretory IgA deficient airways than those with milder disease. The study provides evidence of an acquired defect in mucosal immunity that may contribute to the pathogenesis of COPD including airway remodeling, chronic inflammation and an altered microbiome. Given the recognized association between severity of disease and frequency of exacerbations, these findings may have pathogenic relevance with regard to increased risk of exacerbations.

References

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