Chronic Obstructive Pulmonary Diseases:
Journal of the COPD Foundation

Journal Club

Impact of the IMPACT Trial

Ron Balkissoon, MD, MSc, DIH, FRCPC[1]

Abbreviations: Global initiative for chronic Obstructive Lung Disease, **GOLD**; long-acting muscarinic antagonist, **LAMA**; long-acting beta2-agonist, **LABA**; inhaled corticosteroid, **ICS**; chronic obstructive pulmonary disease, **COPD**; InforMing the Pathway of COPD Treatment, **IMPACT**; umeclidinium, **UMEC**; vilanterol, **VI**; fluticasone furoate, **FF**; T-helper cell type 2, **TH-2**; forced expiratory volume in 1 second, **FEV_1**; hazard ratio, **HR**; confidence interval, **CI**

Citation: Balkissoon R. Journal club. Impact of the IMPACT Trial. *Chronic Obstr Pulm Dis.* 2018;5(3):221-227. doi: https://doi.org/10.15326/jcopdf.5.3.2018.0150

1 Denver, Colorado

Address correspondence to:

Ron Balkissoon, MD, MSc, DIH, FRCPC
balkissoonr@njhealth.org

Introduction

The latest iteration of the Global initiative for chronic Obstructive Lung Disease (GOLD)[1] guidelines emphasizes the use of long-acting muscarinic antagonist /long-acting beta2-agonist (LAMA/LABA) combination therapy as maintenance therapy before triple therapy (inhaled corticosteroid [ICS]/LABA/LAMA) for chronic obstructive pulmonary disease (COPD) patients in the GOLD Group D and before an ICS/LABA combination in Group C. The exception for this is perhaps for those patients who have known, pre-existing asthma or are considered to have an asthma/COPD overlap. This recommendation is predicated on evidence that LABA/LAMA combinations have been shown to improve lung function and reduce symptoms as well as reduce exacerbations for patients who have had 1 or more exacerbation per year[2,3] in combination with the evidence that inhaled corticosteroids increase the risk of pneumonia in at least a subset of individuals with COPD.[4,5] Indeed, there has been a renewed debate regarding the exact role for inhaled corticosteroids in COPD overall. In this issue of the Journal Club we review the pivotal study, "InforMing the Pathway of COPD Treatment (IMPACT) that compares single inhaler triple therapy (LABA/LAMA/ICS) versus the same ICS/LABA in combination versus with the same LABA/LAMA in combination. The major focus of this Journal Club is the IMPACT study and how it helps to inform us regarding the COPD patient population that may be best suited for use of inhaled steroids. I provide the abstracts from additional recent studies that provide additional food for thought on how we might further refine the role for inhaled corticosteroids in COPD patients.

Note: Abstracts are presented in their original, published format and have not been edited to match JCOPDF style.

Abstract 1
Once-Daily Single-Inhaler Triple Versus Dual Therapy in Patients with COPD

Lipson DA, Barnhart F, Brealey N, et al and the IMPACT Investigators. *New Eng J Med.* 2018;378(18):1671-1680. doi: https://doi.org/10.1056/NEJMoa1713901

BACKGROUND:
The benefits of triple therapy for chronic obstructive pulmonary disease (COPD) with an inhaled glucocorticoid, a long-acting muscarinic antagonist (LAMA), and a long-acting β2-agonist (LABA), as compared with dual therapy (either inhaled glucocorticoid-LABA or LAMA-LABA), are uncertain.

METHODS:
In this randomized trial involving 10,355 patients with COPD, we compared 52 weeks of a once-daily combination of fluticasone furoate (an inhaled glucocorticoid) at a dose of 100µg, umeclidinium (a LAMA) at a dose of 62.5µg, and vilanterol (a LABA)

at a dose of 25µg (triple therapy) with fluticasone furoate-vilanterol (at doses of 100µg and 25µg, respectively) and umeclidinium-vilanterol (at doses of 62.5µg and 25µg, respectively). Each regimen was administered in a single Ellipta inhaler. The primary outcome was the annual rate of moderate or severe COPD exacerbations during treatment.

RESULTS:
The rate of moderate or severe exacerbations in the triple-therapy group was 0.91 per year, as compared with 1.07 per year in the fluticasone furoate-vilanterol group (rate ratio with triple therapy, 0.85; 95% confidence interval [CI], 0.80 to 0.90; 15% difference; P<0.001) and 1.21 per year in the umeclidinium-vilanterol group (rate ratio with triple therapy, 0.75; 95% CI, 0.70 to 0.81; 25% difference; P<0.001). The annual rate of severe exacerbations resulting in hospitalization in the triple-therapy group was 0.13, as compared with 0.19 in the umeclidinium-vilanterol group (rate ratio, 0.66; 95% CI, 0.56 to 0.78; 34% difference; P<0.001). There was a higher incidence of pneumonia in the inhaled-glucocorticoid groups than in the umeclidinium-vilanterol group, and the risk of clinician-diagnosed pneumonia was significantly higher with triple therapy than with umeclidinium-vilanterol, as assessed in a time-to-first-event analysis (hazard ratio, 1.53; 95% CI, 1.22 to 1.92; P<0.001).

CONCLUSIONS:
Triple therapy with fluticasone furoate, umeclidinium, and vilanterol resulted in a lower rate of moderate or severe COPD exacerbations than fluticasone furoate-vilanterol or umeclidinium-vilanterol in this population. Triple therapy also resulted in a lower rate of hospitalization due to COPD than umeclidinium-vilanterol. (Funded by GlaxoSmithKline; IMPACT ClinicalTrials.gov number, NCT02164513

Comments

The primary findings from this trial are that single inhaler, triple therapy reduced moderate-to-severe COPD exacerbations and lead to lower rates of hospitalization due to COPD then the LAMA/LABA combination, umeclidinium/vilanterol (UMEC/VI). A recently published study demonstrated no difference (non-inferiority) between the fluticasone furoate (FF)/VI/UMEC inhaler versus FF/VI+UMEC in a separate inhaler.[6] The rate of pneumonia was indeed higher in both of the fluticasone furoate containing arms of the study compared to the UMEC/VI combination. Pneumonias were confirmed by chest x-rays compared to the baseline chest x-rays at the beginning of study. The study also indicated that a triple (FF/VI/UMEC) might play a role in preventing more serious exacerbations that lead to hospitalization as compared to a LAMA/LABA combination. This could be on the basis of the addition of FF alone or also to the proposed synergistic effects of combining ICS and LABA formulations together.

The study also demonstrated that participants with 2 or more moderate-to-severe exacerbations in the previous 12 months were more likely to have a greater reduction in exacerbations if they were on FF (either as FF/VI/UMEC or FF/VI) than if they were on UMEC/VI. The FF/VI/UMEC group had a 11% greater reduction in exacerbation rate compared to FF/VI and a 28% reduction compared to the UMEC/VI group whereas, in the cohort that had at least 1 exacerbation, there was a 21% reduction in exacerbations compared to the UMEC/VI group and a 20% reduction in exacerbations compared to the FF/VI group. Interestingly, this is in keeping with their prior iteration of the GOLD guidelines that had suggested that ICS/LABA was at least an equal choice for those patients that had 2 or more moderate-to-severe exacerbations or 1 hospitalization.

The participant entry criteria in the IMPACT trial did not exclude patients with a prior history of asthma. Previous studies have shown that there is an increased risk of developing COPD for individuals with airway hyper-responsiveness[7] and Christiansen and colleagues[8] noted that approximately 20% of patients in 2 large COPD cohorts demonstrated a T-helper cell type 2 (TH-2) genetic signature and that they appeared to be the best responders to ICS/LABA in those 2 study cohorts. Unfortunately, the authors from the IMPACT study do not provide the number of participants who reported a previous history of asthma. Nonetheless, all patients had to have at least a 10 pack-years smoking history, (about 35% in each treatment arm were current smokers). In addition, 57% had a baseline blood eosinophil count of greater than 150eos/µL and 18% demonstrated at least a 12%/200mL bronchodilator response. This study was designed utilizing the previous GOLD classification scheme that incorporated forced expiratory volume in

1 second (FEV_1). Only 1% had an FEV_1 greater than 80%, 37% between 50% and 80%, 47% between 30% and 50% and 16% had an FEV_1 less than 30%.

The authors did not find any difference in response to triple therapy comparing those with an eosinophil count above versus below 150eos/μL. There remains ongoing debate as to the appropriate cutoff point for eosinophils in terms of absolute eosinophils and in general to the utility of using blood eosinophils to predict responses to ICSs in COPD.[9,10] Even though we are not given the distribution and/or range of eosinophil counts, with further evaluation of the data collected this study may actually be quite helpful in supporting the notion that there is indeed a subset of patients with COPD who benefit from ICSs and that they are individuals who have a history of asthma or T2 type features and/or have 2 or more exacerbations per year.

Though not mentioned in the abstract, the study also showed a reduction in all-cause mortality (including off treatment participants) in the FF/VI/UMEC group (28.6%, hazard ration [HR] 0.71; 95% confidence interval [CI] 0.51-0.99), unadjusted P=0.043) compared to UMEC/VI. The reduction for FF/VI versus UMEC/VI was not statistically significant (20.6% HR 0.79; 95% CI 0.58 to 1.10; P=0.164). The UMEC/VI group had only 2000 participants compared to the 2 steroid containing arms (4000 participants) and this sample size was calculated on the basis of exacerbation data as primary outcome. Hence, one is not able to interpret too much from the mortality signal as it was only a secondary outcome assessment and not even part of the hierarchical statistical analysis of secondary outcomes.

The IMPACT trial is unique and invaluable in that it compared the exact same medications in the same delivery device in different combinations and provides the best data to compare the relative efficacy and safety of dual versus triple combination therapies. The study clearly demonstrated that there remains a role for inhaled corticosteroids in the treatment of patients with COPD and that in some patients it perhaps should be considered before rather than "stepping up" after a LAMA/LABA combination fails to adequately reduce symptoms, improve lung function and/or reduce exacerbations. The Supplementary Appendix for this study has a wealth of data that helps us to further understand the characteristics of those patients who may be appropriate candidates. Unfortunately, much of this information is not presented in the published manuscript. To further tease out the role of triple therapy it would be helpful to know further characteristics of the patients in this study such as total pack-year history, number of patients who met a cut off criteria eosinophil count of 300 or more as well as those who had a prior history of asthma or met criteria for asthma or asthma/COPD overlap. It would be very interesting for the investigators to consider performing a retrospective T2 genetic mutation signature analysis similar to Christiansen.[8] As presented, the data suggest that triple therapy may be more appropriate in the more severe patients (higher exacerbation frequency history) and/or those with underlying asthmatic type characteristics where the additional use of ICSs are of greatest benefit. We do not have enough information from this study to understand what proportion of the patients likely fall into this category. Clearly, for a subset of patients, the risk of pneumonia may very well outweigh the benefits of ICS use but this study reaffirms that there is a group of COPD patients for whom triple therapy is superior to LAMA/LABA combinations and our task is to further study and identify the characteristics that define this population.

Abstract 2
Single-inhaler Triple Therapy in Symptomatic COPD Patients: FULFIL Subgroup Analyses

Halpin DMG, Birk R, Brealey N, et al. *ERJ Open Res.* 2018;4(2):00119-2017.
doi: https://doi.org/10.1183/23120541.00119-2017

Triple inhaled corticosteroid (ICS)/long-acting muscarinic antagonist (LAMA)/long-acting β2-agonist (LABA) therapy is recommended for symptomatic patients with chronic obstructive pulmonary disease (COPD) and at risk of exacerbations. However, the benefits versus side-effects of triple inhaled therapy for COPD, based on distinct patient clinical profiles, are unclear. FULFIL, a phase III, randomised, double-blind study, compared 24 weeks of once-daily fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI) 100/62.5/25μg using the Ellipta inhaler with twice-daily budesonide/formoterol (BUD/FOR) 400/12μg

using the Turbuhaler. Subgroup analyses of forced expiratory volume in 1 s (FEV_1), St George's Respiratory Questionnaire (SGRQ) Total score and exacerbation rates were carried out. Subgroups were defined by COPD medication at screening (ICS+LABA, BUD+FOR, ICS+LABA+LAMA, LAMA alone, tiotropium alone and LAMA+LABA), by disease severity (lung function and exacerbations) and by exacerbation history (exacerbation severity and frequency). In the intent-to-treat population (n=1810) at week 24, FF/UMEC/VI (n=911) versus BUD/FOR (n=899) improved FEV_1 and SGRQ Total score and reduced mean annual exacerbation rates in all disease severity and exacerbation history subgroups. FF/UMEC/VI versus BUD/FOR improved FEV_1 and SGRQ Total score in all medication subgroups and reduced mean annual exacerbation rates in all medication subgroups, except LAMA+LABA. Adverse events were similar across subgroups. These findings support the benefit of FF/UMEC/VI compared with dual ICS/LABA therapy in patients with symptomatic COPD regardless of diseaseseverity or prior treatment and may help to inform clinical decision making.

Comments

This study demonstrates the superiority of triple therapy versus ICS/LABA alone but, unlike IMPACT, it compared different medications and different delivery devices. It does suggest however that the dual bronchodilation does not only impact symptoms and FEV_1 but also reduces exacerbations.

Abstract 3
Intensified Therapy with Inhaled Corticosteroids and Long-Acting β2-Agonists at the Onset of Upper Respiratory Tract Infection to Prevent Chronic Obstructive Pulmonary Disease Exacerbations. A Multicenter, Randomized, Double-Blind, Placebo-controlled Trial

Stolz D, Hirsch HH, Schilter D, et al. *Am J Respir Crit Care Med*. 2018;197(9):1136-1146.
doi: https://doi.org/10.1164/rccm.201709-1807

RATIONALE:
The efficacy of intensified combination therapy with inhaled corticosteroids (ICS) and long-acting β2-agonists (LABA) at the onset of upper respiratory tract infection (URTI) symptoms in chronic obstructive pulmonary disease (COPD) is unknown.

OBJECTIVES:
To evaluate whether intensified combination therapy with ICS/LABA, at the onset of URTI symptoms, decreases the incidence of COPD exacerbation occurring within 21 days of the URTI.

METHODS:
A total of 450 patients with stable, moderate to very severe COPD, were included in this investigator-initiated and -driven, double-blind, randomized, placebo-controlled study. At inclusion, patients were assigned to open-labeled low-maintenance dose ICS/LABA. Each patient was randomized either to intensified-dose ICS/LABA or placebo and instructed to start using this medication only in case of a URTI, at the onset of symptoms, twice daily, for 10 days.

MEASUREMENTS AND MAIN RESULTS:
The incidence of any exacerbation following a URTI was not significantly decreased in the ICS/LABA group, as compared with placebo (14.6% vs. 16.2%; hazard ratio, 0.77; 95% confidence interval, 0.46-1.33; P=0.321) but the risk of severe exacerbation was decreased by 72% (hazard ratio, 0.28; 95% confidence interval, 0.11-0.74%; P=0.010). In the stratified analysis, effect size was modified by disease severity, fractional exhaled nitric oxide, and the body mass index-airflow obstruction-dyspnea, and exercise score. Compared with the stable period, evidence of at least one virus was significantly more common at URTI, 10 days after URTI, and at exacerbation.

CONCLUSIONS:
Intensified combination therapy with ICS/LABA for 10 days at URTI onset did not decrease the incidence of any COPD exacerbation but prevented severe exacerbation. Patients with more severe disease had a significant risk reduction for any exacerbation. Clinical trial registered with www.isrctn.com (ISRCTN45572998).

KEYWORDS:
ICS; LABA; treatment for COPD exacerbations

Comments

This study suggests that more severe exacerbations were reduced. This potentially is not insignificant in terms of additional treatment costs and indirect costs related to missed work, school, etc. The authors did not examine these outcomes. Interestingly, there were no signs of significant, increased side effects with the additional LABA use for 10 days. It is also instructive that there was an association with viral infections and exacerbations.

Abstract 4
Corticosteroid Suppression of Antiviral Immunity Increases Bacterial Loads and Mucus Production in COPD Exacerbations

Singanayagam A, Glanville N, Girkin JL, et al. *Nat Commun*. 2018;9(1):2229.
doi: https://doi.org/10.1038/s41467-018-04574-1

Inhaled corticosteroids (ICS) have limited efficacy in reducing chronic obstructive pulmonary disease (COPD) exacerbations and increase pneumonia risk, through unknown mechanisms. Rhinoviruses precipitate most exacerbations and increase susceptibility to secondary bacterial infections. Here, we show that the ICS fluticasone propionate (FP) impairs innate and acquired antiviral immune responses leading to delayed virus clearance and previously unrecognised adverse effects of enhanced mucus, impaired antimicrobial peptide secretion and increased pulmonary bacterial load during virus-induced exacerbations. Exogenous interferon-β reverses these effects. FP suppression of interferon may occur through inhibition of TLR3- and RIG-I virus-sensing pathways. Mice deficient in the type I interferon-α/β receptor (IFNAR1-/-) have suppressed antimicrobial peptide and enhanced mucin responses to rhinovirus infection. This study identifies type I interferon as a central regulator of antibacterial immunity and mucus production. Suppression of interferon by ICS during virus-induced COPD exacerbations likely mediates pneumonia risk and raises suggestion that inhaled interferon-β therapy may protect.
PMID: 29884817 PMCID: PMC5993715 DOI: 10.1038/s41467-018-04574-1

Comments

This is an interesting animal study that provides insights into potential mechanisms that might predispose some individuals using ICSs to increased risks of pneumonia.

Abstract 5
Role of Eosinophils in Airway Inflammation of Chronic Obstructive Pulmonary Disease

Tashkin DP, Wechsler ME. *Int J Chron Obstruct Pulmon Dis*. 2018;13:335-349. doi: https://doi.org/10.2147/COPD.S152291

COPD is a significant cause of morbidity and mortality. In some patients with COPD, eosinophils contribute to inflammation that promotes airway obstruction; approximately a third of stable COPD patients have evidence of eosinophilic inflammation. Although the eosinophil threshold associated with clinical relevance in patients with COPD is currently subject to debate, eosinophil counts hold potential as biomarkers to guide therapy. In particular, eosinophil counts may be useful in assessing which patients may benefit from inhaled corticosteroid therapy, particularly regarding exacerbation prevention. In addition, several therapies targeting eosinophilic inflammation are available or in development, including monoclonal antibodies targeting the IL5 ligand, the IL5 receptor, IL4, and IL13. The goal of this review was to describe the biologic characteristics of eosinophils, their role in COPD during exacerbations and stable disease, and their use as biomarkers to aid treatment decisions. We also propose an algorithm for inhaled corticosteroid use, taking into consideration eosinophil counts and pneumonia history, and emerging eosinophil-targeted therapies in COPD.

KEYWORDS:
asthma; corticosteroids; lung disease; pneumonia; pulmonary diseases
PMID: 29403271PMCID: PMC5777380

Comments

An interesting review that not only discusses the potential role of anti-eosinophil biologics in COPD but also proposes an algorithm for ICS use in COPD.

References

1. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management and prevention of COPD, 2018. GOLD website. http://goldcopd.org/wp-content/uploads/2017/11/GOLD-2018-v6.0-FINAL-revised-20-Nov_WMS.pdf Published 2018. Accessed July 2018.

2. Bremner PR, Birk R, Brealey N, Ismaila AS, Zhu C-Q, Lipson DA. Single-inhaler fluticasone furoate/umeclidinium/vilanterol versus fluticasone furoate/vilanterol plus umeclidinium using two inhalers for chronic obstructive pulmonary disease: a randomized non-inferiority study. *Respir Res*. 2018; 19(1):19. doi: https://doi.org/10.1186/s12931-018-0724-0

3. Wedzicha JA, Banerji D, Chapman KR, et al for the FLAME Investigators. Indacaterol-glycopyrronium versus salmeterol-fluticasone for COPD. *N Engl J Med*. 2016. 374(23): 2222-2234. doi: https://doi.org/10.1056/NEJMoa1516385

4. Cazzola M, Ora J, Puxeddu E. Dual bronchodilation and exacerbations of COPD. *J Thorac Dis*. 2016. 8(9): 2383-2386. doi: https://doi.org/10.21037/jtd.2016.08.92

5. Bourbeau J, Aaron SD, Barnes NC, Davis KJ, Lacasse Y, Nadeau G. Evaluating the risk of pneumonia with inhaled corticosteroids in COPD: retrospective database studies have their limitations SA. *Respir Med*. 2017;123: 94-97. doi: https://doi.org/10.1016/j.rmed.2016.12.015

6. Suissa S, Patenaude V, Lapi F, Ernst P. Inhaled corticosteroids in COPD and the risk of serious pneumonia. *Thorax*. 2013;68(11):1029-1036. doi: https://doi.org/10.1136/thoraxjnl-2012-202872

7. Kanner RE, Connett JE, Altose MD, et al. Gender difference in airway hyperresponsiveness in smokers with mild COPD. The Lung Health Study. *Am J Respir Crit Care Med*. 1994;150(4): 956-961. doi: https://doi.org/10.1164/ajrccm.150.4.7921469

8. 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(7):758-766. doi: https://doi.org/10.1164/rccm.201408-1458OC

9. Pavord ID, Lettis S, Locantore N, et al. Blood eosinophils and inhaled corticosteroid/long-acting beta-2 agonist efficacy in COPD. *Thorax*. 2016; 71(2): 118-125. doi: https://doi.org/10.1136/thoraxjnl-2015-207021

10. Pascoe S, Pavord I, Hinds D, Locantore N, Barnes N. The association between blood eosinophils and risk and treatment outcome in COPD is not dichotomised. *Lancet Respir Med*. 2018. 6(5):e18. doi: https://doi.org/10.1016/S2213-2600(18)30137-1