Triple therapy in COPD: understanding the data

Samy Suissa [1,2]

[1]Centre for Clinical Epidemiology, Lady Davis Institute–Jewish General Hospital, Montreal, QC, Canada. [2]Department of Epidemiology and Biostatistics, McGill University, Montreal, QC, Canada.

Corresponding author: Samy Suissa (samy.suissa@mcgill.ca)

Shareable abstract (@ERSpublications)
Effectiveness of single-inhaler triple therapy on exacerbation risk and mortality in COPD is exaggerated in IMPACT and ETHOS trials from confounding by prior ICS discontinuation: effectiveness fades in analyses and studies with no prior ICS discontinuation https://bit.ly/3tOgNdW

Cite this article as: Suissa S. Triple therapy in COPD: understanding the data. *ERJ Open Res* 2023; 9: 00615-2022 [DOI: 10.1183/23120541.00615-2022].

Copyright ©The authors 2023

This version is distributed under the terms of the Creative Commons Attribution Non-Commercial Licence 4.0. For commercial reproduction rights and permissions contact permissions@ersnet.org

Received: 14 Nov 2022
Accepted: 15 Nov 2022

The recommended pharmacological treatment for a patient first diagnosed with COPD is a long-acting bronchodilator, either long-acting muscarinic antagonists (LAMA), long-acting β_2-agonists (LABA) or their combination [1]. For patients with high blood eosinophil counts (>300 cells per µL), an inhaled corticosteroid (ICS) combined with a LABA (LABA-ICS) is considered. In follow-up management, dual (LAMA-LABA and LABA-ICS) and triple combinations (LAMA-LABA-ICS) of these drug classes are recommended if these initial treatments become ineffective, according to the degree of dyspnoea and the frequency of exacerbations. Currently, several single-inhaler combinations of these three treatment classes are available, including single-inhaler triple therapy.

A foremost question for the clinician is stepping up treatment from a LAMA-LABA inhaler to triple therapy. Three major trials have compared the effectiveness and safety of various single-inhaler triple therapy agents with single-inhaler dual bronchodilators, particularly LAMA-LABA, on major outcomes in patients with COPD [2–4]. The interpretation of the resulting data from these trials has been challenging.

We briefly review these trials and explain aspects of the study designs to better understand the resulting data. We compare these data to those of a recent real-world observational study assessing the comparative effectiveness of single-inhaler triple therapy *versus* single-inhaler dual bronchodilators.

The randomised trials

The Informing the Pathway of COPD Treatment (IMPACT) trial compared single-inhaler triple therapy (umeclidinium, vilanterol and fluticasone furoate) with its two dual inhalers, a LABA-ICS (vilanterol and fluticasone furoate) and a LAMA-LABA (umeclidinium and vilanterol) over 1 year [2]. It enrolled 10 355 COPD patients with moderate to severe airflow limitation and a recent history of exacerbations, including those with a past diagnosis of asthma. Patients had to discontinue their pre-study treatment at randomisation. Triple therapy was associated with a 25% lower rate of moderate to severe exacerbations and a 42% reduction in all-cause mortality compared with LAMA-LABA [2, 5].

The TRIBUTE trial compared single-inhaler triple therapy (glycopyrronium bromide, formoterol fumarate and beclomethasone dipropionate) with a dual LAMA-LABA bronchodilator (glycopyrronium and indacaterol) over 1 year [3]. The study included 1532 COPD patients with severe to very severe airflow limitation and at least one moderate or severe exacerbation in the year prior. Patients with a past diagnosis of asthma were eligible but those already on triple therapy were not. All patients discontinued their maintenance therapy and switched to the LAMA-LABA comparator during a 2-week run-in before randomisation. Triple therapy was associated with a 15% lower rate of moderate to severe exacerbations compared with the LAMA-LABA comparator.

The Efficacy and Safety of Triple Therapy in Obstructive Lung Disease (ETHOS) trial compared single-inhaler triple therapy (glycopyrrolate, formoterol and budesonide) with its two dual inhalers,

LABA-ICS (formoterol and budesonide) and LAMA-LABA (glycopyrrolate and formoterol) over 1 year [4]. This trial enrolled 8509 COPD patients with moderate to very severe airflow limitation and at least one exacerbation in the past year, including patients with a past diagnosis of asthma. All patients discontinued their maintenance therapy, receiving short-acting bronchodilators during a 2-week run-in, except for ICS, which were continued during the run-in and discontinued at randomisation. Triple therapy was associated with a 24% lower rate of moderate to severe exacerbations and 46% lower mortality compared with LAMA-LABA [4, 6].

The real-world observational study

One observational study has compared the effectiveness of single-inhaler triple therapy with dual bronchodilators in real-world clinical practice [7]. It formed a cohort of COPD patients, treated during 2017–2020, from the UK's Clinical Practice Research Datalink. The cohort included ICS-naïve patients (patients could have used LAMA or LABA, but no ICS) who initiated single-inhaler triple therapy or single-inhaler dual bronchodilators and were followed for 1 year. The incidence of COPD exacerbation and other outcomes was compared, after adjustment by propensity score weighting to render the two treatment arms comparable.

The cohort included 4106 new users of single-inhaler triple therapy and 29 702 of dual bronchodilators. The adjusted hazard ratio (HR) of a first moderate or severe exacerbation with triple therapy relative to dual bronchodilators was 1.08 (95% CI 1.00–1.16). However, the hazard of exacerbation was lower with triple therapy among patients with two or more prior exacerbations, with prior asthma diagnosis and with blood eosinophil count >300 cells per µL. All-cause mortality was increased by 53% with triple therapy, as was severe pneumonia (HR 1.50, 95% CI 1.29–1.75).

Methodological issues

The three randomised trials recruited patients who were already treated with maintenance therapy including LAMA, LABA and ICS, that they had to discontinue to enter the trial. In IMPACT and ETHOS, patients discontinued ICS on the day of randomisation, while in TRIBUTE, discontinuation was followed by a 2-week run-in period on a dual bronchodilator before randomisation. A large proportion of patients discontinued ICS in IMPACT (70%), ETHOS (80%) and TRIBUTE (65%).

An examination of the Kaplan–Meier curves of time to first exacerbation of all three trials shows a clear spike in exacerbation in the first month of follow-up in the arm randomised to LAMA-LABA [2–4]. Indeed, it appears that the beneficial effects of triple therapy, compared with LAMA-LABA, on reducing exacerbations, as well as mortality in IMPACT and ETHOS, were limited to the early period after randomisation, with no benefit observed during the subsequent follow-up [8–10]. Such an early "benefit" is compatible with an effect of abrupt ICS withdrawal at randomisation among those allocated to LAMA-LABA, especially from the inclusion of patients with a history of asthma [11, 12].

Thus, rather than assessing the effect of initiating triple therapy in patients with COPD, the three randomised trials produced a confounded effect, namely a combined effect of discontinuing prior ICS treatment and of starting triple therapy. One solution to this could be a sufficiently long run-in period that would tease out the effects of prior treatment discontinuation [11]. However, the choice of the common treatment during the run-in can possibly also confound the effect [13]. An accurate way of removing such confounding by discontinuation when comparing triple therapy with dual bronchodilators is to enrol only patients treated with a LAMA, LABA or both, but not ICS. Such adaptive selection trial designs tailor the randomisation scheme to the treatment used by a subject at the time of trial enrolment, thus eliminating effects from confounding by treatment discontinuation, such as ICS, at randomisation [14].

The IMPACT and ETHOS trials did report results stratified by prior ICS use. The subgroup not treated with ICS prior to randomisation can thus provide an unconfounded effect of triple therapy compared with a dual LAMA-LABA bronchodilator. This stratified analysis was not reported for the TRIBUTE trial. The observational study, on the other hand, was conducted in ICS-naïve COPD patients at the time of initiating single-inhaler triple therapy or single-inhaler dual bronchodilators, thus inherently avoiding such confounded effects.

Figure 1 displays the HR of a moderate or severe exacerbation with triple therapy relative to dual bronchodilators in IMPACT, ETHOS and the observational study, among patients who were not previously on ICS [7, 15, 16]. The HRs were 0.88 (95% CI 0.76–1.03) and 0.89 (95% CI 0.72–1.08) in IMPACT (HR was not reported, thus was estimated from the reported rate ratio) and ETHOS, respectively. In the observational study, the HR was 0.83 (95% CI 0.74–0.92) among patients with two or more prior

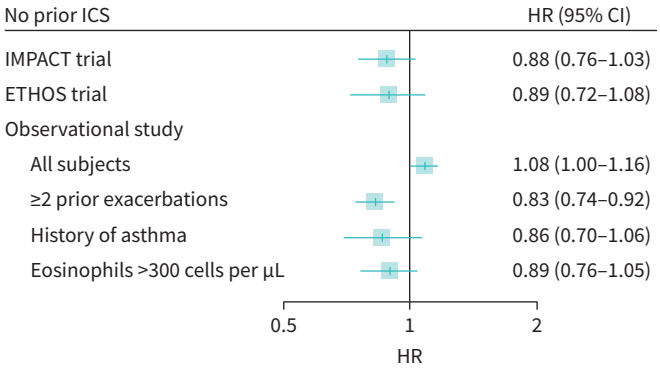

FIGURE 1 Hazard ratio (HR) of a moderate or severe COPD exacerbation comparing single-inhaler triple therapy with single-inhaler dual bronchodilators in patients with COPD in the first year after treatment initiation, among patients with no prior inhaled corticosteroids (ICS), comparing results from the Informing the Pathway of COPD Treatment (IMPACT) and Efficacy and Safety of Triple Therapy in Obstructive Lung Disease (ETHOS) randomised trials, and from the observational real-world study. The HR was not reported in the IMPACT trial and thus was estimated from the reported rate ratio.

exacerbations, while for those with prior asthma diagnosis, it was 0.86 (95% CI 0.70–1.06) and for patients with blood eosinophil count >300 cells per µL it was 0.89 (95% CI 0.76–1.05).

Figure 2 displays the HR of all-cause mortality with triple therapy relative to the dual bronchodilator in IMPACT, ETHOS and the observational study, among patients who were not previously on ICS [5–7]. It shows that among ICS-naïve patients, the HRs of all-cause mortality comparing triple therapy with dual bronchodilators were 1.25 (95% CI 0.60–2.59) in IMPACT and 1.49 (95% CI 0.49–4.55) in ETHOS, compared with 1.53 (95% CI 1.30–1.79) in the observational study.

Conclusion

While the IMPACT, TRIBUTE and ETHOS trials reported significant overall reductions in exacerbation and mortality comparing single-inhaler triple therapy with dual bronchodilators, this reduction was confounded by the effect of discontinuation of prior ICS use at the time of randomisation. The most accurate way to unconfound this effect is to restrict the trial enrolment to ICS-naïve patients prior to randomisation, which would be more challenging to identify but would provide unbiased estimates of the effectiveness. The subgroup analyses among the ICS-naïve patients in these trials, which are substantial at over 3000 in IMPACT and 1700 in ETHOS, show that the hazards of exacerbation with single-inhaler triple therapy are not significantly different from dual LAMA-LABA bronchodilators, though with point estimates are lower than unity. The large real-world observational study of this same question, conducted among the ICS-naïve COPD patients early in their disease, found a significant reduction in the risk of exacerbation with triple therapy only among those with two or more exacerbations prior to treatment. In all studies, mortality was not reduced with triple therapy among the ICS-naïve patients.

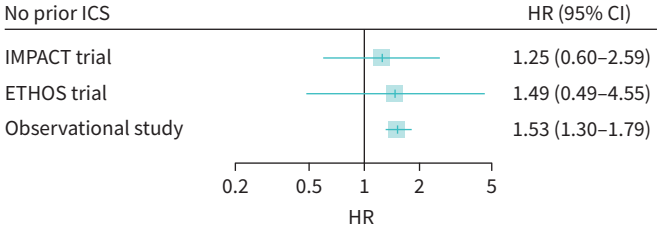

FIGURE 2 Hazard ratio (HR) of all-cause mortality comparing single-inhaler triple therapy with single-inhaler dual bronchodilators in patients with COPD in the first year after treatment initiation, among patients with no prior inhaled corticosteroids (ICS), comparing results from the Informing the Pathway of COPD Treatment (IMPACT) and Efficacy and Safety of Triple Therapy in Obstructive Lung Disease (ETHOS) randomised trials, and from the observational real-world study.

Future randomised trials of COPD treatments could rely on adaptive selection trial designs to avoid effects confounded by prior treatment discontinuation, which clouds their interpretation [14]. In addition, properly conducted observational studies, currently used for regulatory decision-making, can contribute valuable complementary real-world evidence [17, 18]. In the meantime, these unconfounded data analyses suggest that single-inhaler triple therapy should be mainly reserved for patients with multiple exacerbations while, for most others, dual bronchodilators may be just as effective whilst circumventing the excess risk of severe pneumonias with triple therapy, as recommended by the Global Initiative for Chronic Obstructive Lung Disease committee reports [1].

Provenance: Submitted article, peer reviewed.

Conflict of interest: The author attended scientific advisory committee meetings or received speaking fees from AstraZeneca, Atara, Boehringer Ingelheim, Bristol-Myers-Squibb, Merck, Novartis, Panalgo, Pfizer and Seqirus.

Support statement: This study was not funded. S. Suissa is the recipient of the Distinguished James McGill Professorship award.

References

1 Singh D, Agusti A, Anzueto A, *et al.* Global strategy for the diagnosis, management, and prevention of chronic obstructive lung disease: the GOLD science committee report 2019. *Eur Respir J* 2019; 53: 1900164.
2 Lipson DA, Barnhart F, Brealey N, *et al.* Once-daily single-inhaler triple *versus* dual therapy in patients with COPD. *N Engl J Med* 2018; 378: 1671–1680.
3 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, randomised controlled trial. *Lancet* 2018; 391: 1076–1084.
4 Rabe KF, Martinez FJ, Ferguson GT, *et al.* Triple inhaled therapy at two glucocorticoid doses in moderate-to-very-severe COPD. *N Engl J Med* 2020; 383: 35–48.
5 Lipson DA, Crim C, Criner GJ, *et al.* Reduction in all-cause mortality with fluticasone furoate/umeclidinium/vilanterol in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2020; 201: 1508–1516.
6 Martinez FJ, Rabe KF, Ferguson GT, *et al.* Reduced all-cause mortality in the ETHOS trial of budesonide/glycopyrrolate/formoterol for chronic obstructive pulmonary disease. A randomized, double-blind, multicenter, parallel-group study. *Am J Respir Crit Care Med* 2021; 203: 553–564.
7 Suissa S, Dell'Aniello S, Ernst P. Single-inhaler triple *versus* dual bronchodilator therapy in COPD: real-world comparative effectiveness and safety. *Int J Chron Obstruct Pulmon Dis* 2022; 17: 1975–1986.
8 Suissa S, Drazen JM. Making sense of triple inhaled therapy for COPD. *N Engl J Med* 2018; 378: 1723–1724.
9 Suissa S, Ariel A. Triple therapy trials in COPD: a precision medicine opportunity. *Eur Respir J* 2018; 52: 1801848.
10 Suissa S. Perplexing mortality data from triple therapy trials in COPD. *Lancet Respir Med* 2021; 9: 684–685.
11 Wedzicha J, Banerji D, Kostikas K. Single-inhaler triple *versus* dual therapy in patients with COPD. *N Engl J Med* 2018; 379: 590–593.
12 Suissa S, Ernst P, Benayoun B, *et al.* Low-dose inhaled corticosteroids and the prevention of death from asthma. *N Engl J Med* 2000; 343: 332–336.
13 Suissa S. Run-in bias in randomised trials: the case of COPD medications. *Eur Respir J* 2017; 49: 1700361.
14 Suissa S. Triple therapy in COPD: time for adaptive selection trials. *COPD* 2021; 18: 597–601.
15 Han MK, Criner G, Dransfield MT, *et al.* The effect of inhaled corticosteroid withdrawal and baseline inhaled treatment on exacerbations in the IMPACT study. A randomized, double-blind, multicenter clinical trial. *Am J Respir Crit Care Med* 2020; 202: 1237–1243.
16 Singh D, Rabe KF, Martinez FJ, *et al.* Relationship between prior inhaled corticosteroid use and benefits of budesonide/glycopyrronium/formoterol fumarate dihydrate on exacerbations, symptoms, health-related quality of life, and lung function in patients with chronic obstructive pulmonary disease: analyses from the ETHOS study. *Respir Med* 2022; 197: 106857.
17 Sherman RE, Anderson SA, Dal Pan GJ, *et al.* Real-world evidence – what is it and what can it tell us? *N Engl J Med* 2016; 375: 2293–2297.
18 Frieden TR. Evidence for health decision making – beyond randomized, controlled trials. *N Engl J Med* 2017; 377: 465–475.