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The IMPACT of triple *versus* dual single-inhaler therapy on exacerbations of COPD

Journal club

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Commentary on:

Lipson DA, *et al.* Once-daily single-inhaler triple *versus* dual therapy in patients with COPD. *N Engl J Med* 2018; 378: 1671–1680.

Context

For a long time, the combination of an inhaled corticosteroid (ICS) and a long-acting β -agonist (LABA) inhaler agent was considered the mainstay of treating chronic obstructive pulmonary disease (COPD) patients with severe airflow obstruction and frequent exacerbations. More recently, the role of ICS in the treatment paradigm of patients with severe COPD and frequent exacerbations has been challenged. This is mainly driven by: 1) the growing evidence of an increased risk of pneumonia associated with ICS [1]; 2) the introduction of combined dual long-acting bronchodilator inhalation therapy with a long-acting muscarinic antagonist (LAMA) and a LABA therapy as a plausible and likely superior treatment alternative [2];

and 3) the recognition that probably not all COPD exacerbation phenotypes stand to equally benefit from ICS therapy, *e.g.* patients with high blood eosinophil counts probably stand to benefit more from ICS therapy than those with low eosinophil counts [3]. The Informing the Pathway of COPD Treatment (IMPACT) study aimed to address the question of whether ICS in addition to dual therapy with LAMA/LABA can reduce moderate and severe acute exacerbations of COPD (AECOPD) compared with LAMA/LABA therapy alone [4].

Methods

This was a multicentre, randomised controlled trial that included patients aged ≥ 40 years who either had a forced expiratory volume in 1 s (FEV₁) that was $< 50\%$ of the predicted normal value and a history of at least one moderate or severe AECOPD in the previous year, or an FEV₁ of 50–80% of the predicted normal value and at least two moderate or one severe AECOPD in the previous year. The study was conducted in 37 countries. Patients were randomly assigned to one of three treatment



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In the IMPACT trial, triple inhalation therapy resulted in a lower rate of moderate or severe COPD exacerbations compared with either dual therapy with ICS/LABA or LAMA/LABA, but pneumonia rates were increased. <http://ow.ly/pYJn30mgpFp>



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arms: 1) a once-daily triple combination therapy of fluticasone furoate (an ICS) 100 µg, umeclidinium (a LAMA) 62.5 µg and vilanterol (a LABA) 25 µg; 2) a once-daily dual combination therapy of fluticasone furoate 100 µg and vilanterol 25 µg; or 3) a once-daily dual combination therapy of umeclidinium 62.5 µg and vilanterol 25 µg. Each treatment was given in a single dry-powder inhaler (Ellipta, GlaxoSmithKline). The primary outcome was the annual rate of moderate or severe AECOPD during treatment. A mild AECOPD was defined as worsening of symptoms treated with increased salbutamol. A moderate AECOPD was one treated with antibiotics or systemic glucocorticoids, and a severe AECOPD was one resulting in hospitalisation or death.

Main results

Over a 3-year period, 10355 patients were randomised and included in the intention to treat analysis, of which 88% completed the trial. Patients on triple therapy with ICS/LAMA/LABA had a mean of 0.91 moderate or severe AECOPD per year during treatment, compared with 1.07 per year among patients on dual therapy with ICS/LABA and 1.21 per year among patients on dual therapy with LAMA/LABA. This resulted in a rate ratio of 0.85 (95% CI 0.80–0.90) when comparing ICS/LAMA/LABA with ICS/LABA therapy and a rate ratio of 0.75 (95% CI 0.70–0.81) when comparing ICS/LAMA/LABA with LAMA/LABA therapy. Therefore, the rate of moderate and severe AECOPD was significantly lower with ICS/LAMA/LABA therapy than with ICS/LABA or LAMA/LABA therapy. This effect was observed regardless of eosinophil level, although a greater reduction in the rate of moderate or severe AECOPD in patients on an ICS compared with those not receiving an ICS was observed in patients with eosinophil levels of ≥ 150 cells· μL^{-1} . The annual rate of AECOPD was 0.95 (95% CI 0.90–1.01) with ICS/LAMA/LABA therapy, 1.08 (95% CI 1.02–1.14) with ICS/LABA therapy, and 1.39 (95% CI 1.29–1.51) with LAMA/LABA therapy in patients with eosinophil levels of at least 150 cells· μL^{-1} .

All-cause mortality was significantly lower in the groups that received an ICS compared with the LAMA/LABA group (50 patients, 1%, in the triple therapy group, 49 patients, 1%, in the ICS/LABA group and 39 patients, 2%, in the LAMA/LABA group).

The rate of pneumonia was significantly higher in the groups that received an ICS compared with the LAMA/LABA group (9.6 and 9.7 *versus* 6.1 pneumonias per 100 patient-years in the ICS/LAMA/LABA, ICS/LABA and LAMA/LABA groups, respectively).

Commentary

This study showed that triple inhalation therapy resulted in a significantly lower rate of moderate or severe COPD exacerbations than either dual therapy with ICS/LABA or LAMA/LABA. The certainty in the

evidence provided by this study is lowered by features of the study design and the included study population. Many of the patients assigned to the LAMA/LABA group were stepping down in their treatment and had ICS abruptly withdrawn at the time of randomisation, which could have triggered an AECOPD. Also, patients with a history of asthma were included, which could explain the very high rates of AECOPD in the first month after randomisation in the LAMA/LABA group [5]. Thus, the benefit of triple therapy in comparison to LAMA/LABA therapy might have been overestimated in the IMPACT study. As outlined by the authors of the study, these study features probably also explain why the findings stand in contrast to those of the FLAME trial, which showed a benefit of LAMA/LABA over inhaled ICS/LABA therapy [2].

Of note, however, the TRIBUTE trial which was published in early 2018, and included 1532 patients in 17 countries, also showed that a single-inhaler triple combination of beclomethasone dipropionate, glycopyrronium and formoterol fumarate (ICS/LABA/LABA) significantly reduced the rate of moderate and severe AECOPD compared with a single-inhaler dual bronchodilator combination of glycopyrronium and indacaterol (LAMA/LABA) [6]. This effect was observed despite the fact that the TRIBUTE study excluded patients who were already on triple therapy, meaning that there was no step down in treatment, and also excluded patients with a current diagnosis of asthma.

In the IMPACT study, all-cause mortality was lower in the groups that received an ICS, but the study was not powered for this outcome, and the results should therefore be interpreted with caution, especially as they differ from the findings of the SUMMIT study [7]. The SUMMIT study was powered for the outcome of all-cause mortality and did not show a benefit in all-cause mortality when adding an ICS to a LABA (fluticasone furoate/vilanterol compared with vilanterol).

A recently published pooled analysis of mortality reported as safety outcome (as opposed to mortality reported as an efficacy outcome) in three landmark studies in patients with severe and very severe COPD found that the risk of non-respiratory mortality was significantly reduced with extrafine ICS-containing treatments compared with ICS-free treatments (hazard ratio 0.65; 95% CI 0.43–0.97) [8]. The authors argued that this potentially points towards a positive effect of ICS on comorbidities associated with COPD. The pooled analysis was, however, not based on a systematic review, and the limited focus on mortality reported as adverse outcome, while ignoring mortality reported as efficacy outcome, is problematic.

In the IMPACT study, the risk of pneumonia was significantly increased in patients on ICS treatment but was not associated with an increase in all-cause mortality in patients on ICS treatment, as outlined above. This finding is consistent with the result of a systematic review that found an increased relative risk of pneumonia of 1.61 (95% CI 1.35–1.93)

associated with ICS treatment in COPD patients in 29 randomised controlled trials but no increase in all-cause mortality (relative risk 0.95; 95% CI 0.85–1.05) [1]. It has been speculated that ICS could have a dual effect: an adverse effect from the immunosuppressive properties of ICS and a mitigating effect from the anti-inflammatory properties of ICS [9]. While the immunosuppressive effects increase the risk of pneumonia, it is possible that the anti-inflammatory effects of ICS reduce the severity of an episode of pneumonia and therefore the pneumonia case fatality.

Implications for practice

Clinicians should only consider triple therapy in symptomatic patients with COPD who

have frequent AECOPDs despite maximised bronchodilator therapy with a LAMA/LABA combination, as recommended by the 2018 Global Initiative for Chronic Obstructive Lung Disease guidelines [10]. The potential benefit of reduced exacerbation frequency with ICS/LAMA/LABA treatment compared with LAMA/LABA treatment has to be weighed against the increased risk of pneumonia. COPD patients who are potentially eligible for ICS treatment based on the severity of their disease and frequent exacerbations, should be informed about potential benefits as well as harms of ICS treatment by the treating clinician. The patient and clinician should then determine together the best course of action for an individual patient taking into account the patient's informed preferences.

Conflict of interest

C.C. Dobler has nothing to disclose.

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