Triple therapy has an impact in COPD!

The debate on the optimal therapy for severe chronic obstructive pulmonary disease (COPD) has long been characterised by divided opinions, with the central point of dispute being whether or not an inhaled corticosteroid (ICS) provides additional benefit over a long-acting beta agonist/long-acting muscarinic antagonist (LABA/LAMA) combination, and in which patients their uses are appropriate. One camp cites the FLAME (effect of indacaterol/glycopyrronium v. fluticasone/salmeterol on COPD exacerbations) study and its supporting literature as evidence that exacerbation reduction from the LABA/LAMA combination is superior to that provided by a LABA/ICS combination.[1,2] Additionally, concerns have been raised about the increased rate of pneumonia in COPD patients treated with ICS, which was first identified by the TORCH (towards a revolution in COPD health) study and later confirmed by post-hoc analyses of other large cohorts.[3,4] Other clinicians will reference the WISDOM (withdrawal of inhaled steroids during optimised bronchodilator management) trial and similar studies, which identified an increase in exacerbations and potentially accelerated decline in lung function when ICS therapy was withdrawn.[5,6] The discussion becomes further nuanced when considering the eosinophilic phenotype of COPD, with the literature (mostly post hoc analyses) suggesting that this subset of patients may have not only experienced symptomatic benefits and exacerbation reduction, but also reduction in lung function decline when treated with an ICS.[7] The current international guidelines recommend only initiating so-called 'triple therapy' with LABA/LAMA/ICS in patients with severe symptoms as well as exacerbations (GOLD (Global Initiative for Obstructive Lung Disease) D classification).[8] A large, randomised and controlled trial directly comparing triple therapy with dual bronchodilator therapy (LABA/LAMA) has long been awaited,[9] and the recently published IMPACT (informing the pathway of COPD treatment) study has met all these criteria.[10] IMPACT was a three-group randomised trial involving over 10 000 patients, most of whom fell into the GOLD D category and were followed over 1 year. The study directly compared triple therapy (vilanterol/umeclidinium/fluticasone fuorate) with LABA/ICS (vilanterol/fluticasone fuorate) and LAMA/LABA (umeclidinium/vilanterol), all administered once daily via a single dry-powder inhaler. The data showed a 25% reduction in exacerbations in patients who were on triple therapy, compared with those who received LABA/LAMA. This difference was even more pronounced in the eosinophilic group of patients, where the reduction in the annual rate of moderate or severe exacerbations was 44%. As expected, there was a small increase in the incidence of pneumonia in the groups treated with ICS, with an absolute increase in incidence of 3% in the triple-therapy group, compared with those on bronchodilators alone. The change in trough FEV_1 from baseline was significantly larger in the triple-therapy group than both other groups, and the data suggest that both the LAMA and ICS components contributed to this difference, with the latter augmenting the effect of the bronchodilators. Although none of the lung function differences reached the 100 mL value of the minimal clinically important difference, the change in St George's Respiratory Questionnaire (SGRQ) score reached clinical significance, in the triple-therapy group only. Lastly, and perhaps most importantly, all-cause mortality was significantly lower in the ICS-containing groups than the LABA/LAMA group, with a hazard ratio of 0.58 for triple therapy and 0.61 for LABA/ICS. IMPACT provides good evidence for the step-up to triple therapy in this patient population, and particularly in patients with blood eosinophilia – unless there is a high risk or previous history of pneumonia. It will be interesting to see how the debate evolves in this important disease arena.

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