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Early View

Research letter

Inhaled corticosteroid containing combinations and mortality in COPD

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Inhaled corticosteroid containing combinations and mortality in COPD

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There is no solid evidence that any pharmacologic treatment reduces mortality in COPD. Two large trials with mortality as an efficacy outcome have been carried out testing a combination of a long-acting beta-agonist (LABA) and an inhaled corticosteroid (ICS) and in both, the reduction in mortality failed to reach statistical significance (1, 2). This could be seen as proof of absence of effect, but given that the TORCH trial (1) resulted in a Hazard Ratio of 0.825 (95% confidence interval 0.681-1.002, p=0.052) for the comparison of combined fluticasone propionate and salmeterol with placebo, the interpretation may not be that simple. The other negative trial, the SUMMIT trial (2), only included patients with moderate COPD and increased risk of cardiovascular comorbidity.

In contrast, when mortality was studied as a safety outcome in severe and very severe COPD patients receiving salmeterol in combination with fluticasone propionate experienced fewer deaths than those receiving the long-acting muscarinic receptor antagonist (LAMA) tiotropium in the INSPIRE trial (3). Also, in the very recent large IMPACT study (4) using a single inhaler in the 3 treatment arms, Lipson et al reported a significant mortality reduction in COPD patients at high risk of exacerbations (55% had ≥ 2 moderate or severe exacerbations and 26% had ≥1 severe exacerbation in the last year) treated with LABA/ICS or LABA/LAMA/ICS combinations compared to a dual LABA/LAMA combination. In both studies, the lower mortality was seen despite an increased risk of pneumonia in the ICS containing arms.

To further explore the potential effect of ICS containing combinations in a single inhaler on mortality, we performed a stratified safety pooled analysis of all fatal adverse events (AEs) comparing extrafine ICS-containing combinations versus ICS-free treatments in 3 recent 52-week studies conducted in patients with severe to very severe COPD at increased risk for exacerbations (≥ 1 moderate or severe exacerbation in the last year). These are currently the only long-term studies comparing the fixed combination of extrafine beclometasone dipropionate (BDP),

formoterol fumarate (FF), and glycopyrronium (G) to 1) extrafine BDP/FF (5), 2) tiotropium or extrafine BDP/FF + tiotropium in a separate inhaler (6), or 3) indacaterol/glycopyrronium bromide (IND/GB) (7). We had full access to these data and included them in our analysis.

When comparing time to death from pooled data for all extrafine ICS containing treatments versus ICS-free treatments, there was a numerical but not statistically significant reduction in the risk of developing a fatal event, Hazard Ratio (HR) 0.71 (95% confidence interval (CI) 0.50-1.02, p=0.066) (Table 1). This can be translated into a number needed to treat (NNT) of 121 patients treated for one year to prevent one death; calculation of NNT based on the survival probability at 52 weeks in the control group from Kaplan-Meier analysis and on the HR (8). A similar effect was seen when comparing only BDP/FF/G vs ICS-free treatments (Table 1). In addition, we found no differences between treatments for respiratory fatal events (HR: 1.01, 95% CI: 0.45-2.22, p=0.989), whereas we found that the risk of non-respiratory fatal events was significantly reduced with extrafine ICS-containing treatments vs ICS-free treatments, (HR: 0.65, 95% CI: 0.43-0.97, p=0.037) (Table 1); i.e., a NNT of 120 patients treated for one year to prevent one death from non-respiratory causes.

Albeit non statistically significant, our findings could suggest that extrafine ICS-containing medications compared to ICS-free treatments may be associated with a lower mortality in symptomatic COPD patients at risk for exacerbations. Interestingly, the only statistically significant effect is on death due to non-respiratory causes, suggesting that a more intense therapy containing an ICS may have a direct or indirect effect on the several and relevant chronic diseases that almost invariably are associated with particularly severe symptomatic COPD (9). This could be due to cardiovascular events, being less likely if the underlying COPD is more stable; indirect evidence for this comes from studies showing a close link between exacerbations and acute coronary events

(10,11). It is also in line with the results of recent managed care studies suggesting that treating COPD and concomitant chronic diseases may improve survival (12).

Our analysis has limitations. It is not trivial whether mortality is an efficacy outcome or a safety outcome. In mortality studies, the aim is always to have complete follow-up of all patients to ensure their vital status at the end of the study. In contrast, adverse events were followed up only for two weeks after the last study drug intake. Thus, we cannot preclude that the effect seen is biased by this incomplete follow-up. In addition, there was no adjudication of cause of death in any of the studies included in this analysis.

Nevertheless, given the unidirectional effects seen in this analysis and the 4 previously cited studies (1-4), there may be cause for more optimism regarding the effect of more intense ICS-containing treatments on survival in symptomatic severe and very severe COPD patients, particularly considering that combination therapy, and especially triple therapy, is almost invariably required in these patients either to improve symptoms, quality of life, and/or to reduce, exacerbations, and hospitalizations. Of course, a properly designed and powered new study with mortality as primary outcome in these patients is required for this optimism to be confirmed.

Table 1. Patients (%) with fatal events and hazard ratios for the treatment group comparisons in TRILOGY, TRINITY and TRIBUTE

	Test (no. of patients)	Comparator (no. of patients)	No. of patients with fatal events (%) Test	No. of patients with fatal events (%) Comparator	Hazard ratio (95% CI), p-value
SINGLE STUDIES					
TRILOGY	BDP/FF/G (N=687)	BDP/FF (N=680)	15 (2.2%)	16 (2.4%)	-
TRINITY	BDP/FF/G (N=1077)	TIO (N=1076)	20 (1.9%)	29 (2.7%)	-
	-	BDP/FF+TIO (N=537)	-	8 (1.5%)	-
TRIBUTE	BDP/FF/G (N=764)	IND/GB (N=768)	16 (2.1%)	21 (2.7%)	-
POOLED ANALYSIS (ALL EVENTS)					
TRILOGY, TRINITY, TRIBUTE	BDP/FF/G, BDP/FF, BDP/FF+TIO (N=3745)	TIO, IND/GB (N=1844)	75 (2.0%)	50 (2.7%)	0.71 (0.50-1.02) p=0.066
	BDP/FF/G (N=2528)	TIO, IND/GB (N=1844)	51 (2.0%)	50 (2.7%)	0.72 (0.49-1.06) p=0.096
POOLED ANALYSIS (NON-RESPIRATORY EVENTS)					
TRILOGY, TRINITY, TRIBUTE	BDP/FF/G, BDP/FF, BDP/FF+TIO (N=3745)	TIO, IND/GB (N=1844)	56 (1.5%)	41 (2.2%)	0.65 (0.43-0.97) p=0.037
POOLED ANALYSIS (RESPIRATORY EVENTS)					
TRILOGY, TRINITY, TRIBUTE	BDP/FF/G, BDP/FF, BDP/FF+TIO (N=3745)	TIO, IND/GB (N=1844)	19 (0.5%)	9 (0.5%)	1.01 (0.45-2.22) p=0.989

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