JOURNAL ROUND-UP

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A review of the TORCH study

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Calverley PMA *et al* for the TORCH investigators. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. *N Engl J Med* 2007;356:775-89.

It has been over a year since the influential TORCH study was published. Nevertheless, the editors thought it appropriate to provide a critical review of the data since there is a great deal of useful information that can still be gleaned from this paper. Mortality was the chief endpoint of the TORCH study, which is very significant since COPD will be the third most common cause of death by 2020.¹

6112 patients were randomised and double-blinded into four treatment groups: salmeterol 50 mcg plus fluticasone propionate at a dose of 500 mcg twice daily administered via a single inhaler discus (SAL/FP); placebo; salmeterol (SAL) alone; or fluticasone (FP) alone. Treatment was for a period of three years. The primary outcome was death from any cause. Other outcomes included exacerbations (defined as a symptomatic deterioration requiring treatment with antibiotic agents, systemic corticosteroids, hospitalisation, or a combination of these), health status assessed by the St. George's Respiratory Questionnaire, and spirometry.

Recruited patients were current or former smokers with at least a 10 pack-year history, aged 40-80, with a previous diagnosis of COPD. The pre-bronchodilator FEV₁ had to be <60% of predicted, with a ratio FEV₁/FVC ≤ 0.70. The post-400 mcg albuterol FEV₁ could not increase more than 10%. Before the two-week run-in period, all use of corticosteroids and inhaled long-acting bronchodilators was stopped, but patients could continue other medications for COPD (note that this study predated the availability of tiotropium). Patients were seen every 12 weeks, with health status and post-bronchodilator spirometry done every 24 weeks.

There were 875 deaths – 12.6% in the combination therapy group, 15.2% in the placebo group, 13.5% in the salmeterol group and 16% in the fluticasone group. The hazard ratio for death in the combination-therapy vs the

placebo group, was 0.825 (95% confidence interval [CI], 0.681 to 1.002; P=0.052, adjusted for the interim analyses), corresponding to a difference of 2.6 percentage points or a reduction in the risk of death of 17.5%. The mortality rate for salmeterol alone or fluticasone propionate alone did not differ significantly from that for placebo. This p value (0.052) was not considered statistically significant, but there was a 17.5% relative reduction in mortality and 2.6% absolute reduction in mortality.

Analysis of all-cause mortality with 3-year interaction tests showed that there was no interaction between survival and multiple factors, including smoking status, region, predicted FEV₁ (%), age, gender, ethnic origin, or body mass index (BMI). Thus, the survival benefit seen in the TORCH trial is similar regardless of any of these interactions.

The combination regimen reduced the annual rate of exacerbations from 1.13 (placebo group) to 0.85, and improved health status and spirometric values (P<0.001 for all comparisons with placebo). A safety sub-study at 88 sites in the USA – with annual assessments of bone mineral densitometry, slit-lamp eye examination and cortisol secretion – was carried out in 658 patients, and showed no differences between the placebo and treatment arms.²

There seemed to be a higher rate of pneumonia in all groups using fluticasone (19.6% in Sal/FP and 18.3% in the FP groups vs placebo (12.3%, P<0.001). It should be noted that pneumonia did not have to be proven by chest radiography, so some of these 'pneumonia' episodes were likely exacerbations, and the rate of exacerbations (and mortality) was clearly lower.

Commentary

The primary outcome was not met since the improvement in mortality did not meet statistical significance. However, one suspects that the signal seen in this study is real. This message has been reiterated in the INSPIRE study (reviewed on page 255), although in the INSPIRE study, powering also prevented statistical significance. The number needed to treat over three years was 39. The data regarding the increased rate of pneumonia in the steroid-treated group seem to be real.³⁻⁵

There are a few reasons that are postulated to have caused the lack of statistical significance. Firstly, the data from the SMART study⁶ showed that asthma patients having monotherapy with salmeterol had an increased mortality compared to those patients treated with additional inhaled

Figure 1. Overall causes of death in COPD.

corticosteroids (ICS). This necessitated an unblinding early on in the study, which decreased the power of the study statistically.

Secondly, the powering of the study was based on the mortality observed in the post hoc analysis of the ISOLDE study,⁷ which was much higher than that seen in the subsequent placebo arm of TORCH.

Thirdly, this was an intention to treat analysis. There was a high withdrawal rate, particularly in the placebo group, and these patients were then free to receive active therapy, thereby narrowing the gap between the treatment arm and the placebo arm of the study.

Nevertheless, this study does provide us with a wealth of knowledge. A comprehensive review panel attempted to adjudicate the cause of death in all the patients who died. Figure 1 shows the causes of death and highlights the significant co-morbidity that we see in patients with COPD.

There was a statistical difference in mortality at three years between those treated with SAL/FP vs FP alone. This has not been shown before,^{8,9} but suggests a likely truism – that there is little value in treating with ICS alone in COPD. This has long been postulated to be due to the difference in the type of inflammation – eosinophilic inflammation in asthma, and neutrophilic inflammation in COPD. However, there are benefits with ICS treatment in terms of reduction in exacerbation rate^{4,7} telling us that the ICS is valuable in this respect but that we should use ICS in a combination inhaler.

COPD exacerbation reduction: which patients?

We have evidence from a number of studies on the reduction of exacerbations in patients with COPD. Each study has had different inclusion points. Kardos *et al* showed a 35% decrease in COPD exacerbations between SAL/FP and SAL,

but only in patients with an FEV₁ of less than 50% who had had two documented exacerbations in the preceding year.¹⁰

In the TORCH study, the FEV₁ needed to be less than 60% for the patient to be included, and values ranged from 32 to 57%. The Optimal study showed only an improvement in severe exacerbations and hospitalisations, and their inclusion criteria was an FEV₁ of less than 65%.¹¹

Clearly the jury is out on when to start ICS (in the form of a combination ICS/long-acting β_2 -agonist inhaler) in COPD patients, but there is evidence of improving quality of life and improved FEV₁, and at the least a reduction in hospitalisation for severe COPD exacerbations, in patients with an FEV₁ <65% predicted when treated with SAL/FP. As far as I'm aware, there is no evidence for the use of ICS in patients with mild COPD. Clearly, this makes it important to classify the severity of the disease in COPD patients.

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doi:10.3132/pcrj.2008.00026

Available online at <http://www.thepcrj.org>