

Research Review

Salmeterol/fluticasone propionate (Seretide™) in COPD

Extended listing for salmeterol/fluticasone propionate in COPD

In New Zealand, salmeterol/fluticasone propionate (SFC) (Seretide™) has recently been granted a licence extension for use in a broader population of patients with chronic obstructive pulmonary disease (COPD); for the symptomatic treatment of patients with moderate to severe COPD (pre-bronchodilator FEV_1 <60% predicted normal) who have significant symptoms despite bronchodilator therapy. SFC is also now indicated for the reduction of all-cause mortality in patients with moderate to severe COPD.

These are significant changes to the treatment options for COPD. The new indications enable a wider application of SFC in COPD treatment and supporting data suggests greater efficacy than previously realised. The following review examines recent major studies that provide evidence to qualify these new indications and explain the rationale for change.

For information about current SFC funding criteria, refer to the pharmaceutical schedule at www.pharmac.govt.nz.

Chronic Obstructive Pulmonary Disease

Chronic obstructive pulmonary disease (COPD) is a major public health problem, a cause of poor health and death worldwide and a significant contributor to healthcare costs and comorbidity²⁻⁴. COPD causes approximately 1.3 million deaths annually, and in 2006, the disease resulted in 12 million disability-adjusted-life-years⁵. In New Zealand, COPD ranks third among the most common causes of death in males and fourth in women⁶. COPD has been estimated to cost the New Zealand community an estimated \$102–\$192 million annually⁷.

Current Treatment Approaches

COPD is considered to be irreversible and relatively resistant to treatment, although it is possible to improve quality of life, increase exercise capacity, and reduce morbidity and mortality; proven pharmacotherapies for COPD include long-acting beta-agonists (LABAs) (e.g. salmeterol), long-acting anticholinergics (e.g. tiotropium), and inhaled corticosteroids (ICSs; e.g. fluticasone propionate).

Many patients with COPD experience periodic worsening of their symptoms, reflecting an acute worsening in lung function⁸ and airway inflammation secondary to viral and/or bacterial infection^{9,10}. These exacerbations contribute to impaired health status^{11,12}, increased hospitalisation costs¹³ and predict mortality¹⁴.

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) treatment aims include the prevention of disease progression, relief of symptoms, improvement of exercise tolerance and of health status, the prevention and treatment of complications and exacerbations and the reduction of mortality¹⁵. Recommended management strategies include initial and ongoing assessment, including spirometry, with supportive therapy to reduce risk factors such as smoking¹⁵.

Pharmacotherapies should be initiated with nonpharmacological/pulmonary rehabilitation programmes, to optimise function through symptom relief, and to prevent or treat aggravating factors and complications¹⁶. In particular, preventing and treating exacerbations is a key treatment goal¹⁵. Bronchodilators, including beta₂-agonists, anticholinergics, theophylline or combinations of these are the recommended first-line pharmacotherapies for COPD¹⁵. Inhaled corticosteroids are indicated for patients with a documented response or those who have severe COPD with frequent exacerbations¹⁵.

According to recent clinical trial evidence, combining a corticosteroid and a LABA in one inhaler for COPD may provide some additional benefits (clinically meaningful differences in quality of life, symptoms and exacerbations) relative to respective monotherapies¹⁷.

The GOLD diagnostic criteria for COPD

A major objective of GOLD is to increase awareness among health care providers and the general public of the significance of COPD symptoms. The classification of severity of COPD includes four stages classified by spirometry, as given below. A fifth category – *Stage 0: At Risk* – that appeared in the 2001 GOLD Report is no longer included as a stage of COPD, as there is incomplete evidence that those patients who meet the definition of “At Risk” (symptoms of chronic cough and sputum production may be present, but spirometry readings are normal) necessarily progress on to *Stage 1: Mild COPD*. Nevertheless, the importance of the public health message that chronic cough and sputum are not normal is unchanged and their presence should trigger a search for underlying cause(s).

Stage 1: Mild COPD. Mild airflow limitation ($FEV_1/FVC < 70\%$, $FEV_1 \geq 80\%$). Patients may or may not have chronic cough and increased sputum production. At this stage, the individual may not be aware that his or her lung function is abnormal.

Stage 2: Moderate COPD. Moderately severe airflow limitation ($FEV_1/FVC < 70\%$; $50\% \leq FEV_1 < 80\%$ predicted). Patients with stage-2 disease often are symptomatic, seek medical attention, and have shortness of breath with exertion.

Stage 3: Severe COPD. Severe airflow limitation ($FEV_1/FVC < 70\%$; $30\% \leq FEV_1 < 50\%$ predicted). At this stage, patients have greater shortness of breath, reduced exercise capacity, and repeated exacerbations which have an impact on patients' quality of life.

Stage 4: Very Severe COPD. Very severe airflow limitation ($FEV_1/FVC < 70\%$; $FEV_1 < 30\%$ predicted) or $FEV_1 < 50\%$ predicted plus chronic respiratory failure or right heart failure. Patients may have *Very Severe* (Stage 4) COPD even if the FEV_1 is $> 30\%$ predicted, whenever these complications are present. At this stage, quality of life is very appreciably impaired and exacerbations may be life-threatening.

Salmeterol/fluticasone propionate (Seretide™) review of new indication data

Stepped care approach recommended for stable COPD

It is generally held that COPD treatments improve symptom control, exacerbations, health status and exercise tolerance, but they fail to modify the long-term decline in lung function^{15,16}.

Clinical guidelines recommend a stepped care approach^{15,16}:

- Step 1:** intermittent short-acting bronchodilators (beta₂-agonist or anticholinergic) as needed.
- Step 2:** Regular inhaled bronchodilators (short and/or long-acting anticholinergic with or without a short and/or long-acting beta₂-agonist). Treatment should be discontinued if there is no clinically significant response after 4–8 weeks.
- Step 3:** an inhaled corticosteroid is recommended for patients with: FEV₁ ≤50% of predicted normal and/or more than 2 exacerbations per year requiring treatment with antibiotics or oral corticosteroids. Treatment should be discontinued if there is no clinically significant response after 4–8 weeks.

Identifying patients with COPD

Differentiating between COPD and other disease states is difficult, given the lack of specific and consistent diagnostic criteria. For instance, many patients with chronic asthma meet the diagnostic criteria for COPD, reflecting patients with asthma whose airway obstruction is not fully reversible. In basic terms, patients who have shortness of breath, chronic cough or sputum production may have COPD, especially if they are aged 45 years or more and have a history of current or former smoking. Adult-onset asthma in current or former smokers is unusual; patients with this apparent presentation will almost certainly have COPD. Asthma is usually reversible (an increase in FEV₁ of 12% or more after inhalation of 400 µg of salbutamol) whereas COPD is characterised by airway obstruction that is not fully reversible (an increase in FEV₁ of <5% after inhalation of 400 µg of salbutamol). Asthma symptoms vary considerably, even on a day-to-day basis, whereas COPD is a slowly progressive disease. Patients with asthma often have a history of other allergic disorders, such as allergic rhinitis or eczema. Patients with asthma often have a history

of asthma in their family. The response to inhaled corticosteroid therapy is usually large and even dramatic in patients with asthma, whereas improvements in COPD are modest.

Table 1. Available SFC products in New Zealand for COPD

Salmeterol/Fluticasone propionate doses (µg/µg)	Formulation
25/50	MDI
25/125	MDI
25/250	MDI
50/100	DPI (Accuhaler™)
50/250	DPI (Accuhaler™)

MDI = metered-dose inhaler; DPI = dry powder inhaler.

of asthma in their family. The response to inhaled corticosteroid therapy is usually large and even dramatic in patients with asthma, whereas improvements in COPD are modest.

Guidelines

1. The National Asthma Council Australia Asthma Management Handbook, <http://www.nationalasthma.org.au/html/home/index.asp>.
2. GOLD pocket guide to COPD diagnosis, management, and prevention, www.goldcopd.org.
3. The guidelines for the management of chronic obstructive lung disease, Australian and New Zealand COPD reference site (<http://www.copdx.org.au/guidelines/index.asp>).
4. The National Institute for Health and Clinical Excellence guidelines for the management of chronic obstructive pulmonary disease in adults in primary and secondary care (<http://guidance.nice.org.uk/CG12/?c=91527>).

Summary of new data for SFC

For the SFC metered-dose inhaler, the recommended starting dose for adults is 2 inhalations 25/125 µg twice daily. For patients who require additional symptomatic control, the 25/125 µg strength may be replaced with the 25/250 µg strength. The maximum daily dose is 2 inhalations 25/250 µg twice daily; at this dose, SFC has been shown to reduce all-cause mortality¹.

For the SFC Accuhaler™, the recommended starting dose for adult patients with COPD is 1 inhalation 50/250 µg twice daily. The 50/250 µg strength may be replaced with the 50/500 µg strength for those patients requiring additional symptomatic control. The maximum daily dose is 1 inhalation of 50/500 µg twice daily; at this dose, SFC has been shown to reduce all-cause mortality^{20,22}.

The wider application for SFC was approved following a regulatory review of studies including the landmark TORCH (TOwards a Revolution in COPD Health) study; the largest prospective, randomised, placebo-controlled pharmacotherapy study ever carried out in COPD²⁰. In addition to a relative risk reduction in mortality of 17.5% (p=0.052), which was just outside the predetermined level of statistical significance of p<0.05, TORCH showed that SFC significantly reduced the rate of exacerbations compared to placebo and that patients treated with SFC showed an improvement in health-related quality of life and FEV₁, when compared with patients receiving placebo, over the three years of the study.

The all-cause mortality findings from TORCH were further supported by data from another study, INSPIRE, a 2-year randomised, double-blind study comparing the effects of SFC 50/500 µg twice daily with tiotropium 18 µg once daily in COPD patients with post-bronchodilator FEV₁ <50% predicted normal²². In INSPIRE, SFC significantly reduced the risk of mortality at any time on therapy over the 2-year study period compared to tiotropium (p=0.012).

Conclusion

SFC may be considered in moderate to severe COPD with symptoms that are poorly controlled despite regular bronchodilator therapy. SFC has been shown to improve FEV₁, and reduce acute exacerbations to a greater extent than either salmeterol or fluticasone propionate given alone in moderate to severe COPD. Additional benefits associated with SFC include sustained beneficial effects on health-related quality of life and reduced mortality. Treatment with combination SFC in one inhaler has the potential to increase patient compliance, compared with the same components in separate inhalers. Details about these effects are reviewed in the clinical trials summarised in the following section.

About the reviewers

Dr Shaun Holt

Dr Holt founded medical trials company P3 Research. He is also an advisor to the Asthma and Respiratory Foundation and the principal medical advisor to Research Review.

Professor Richard Beasley

Professor Beasley is a respiratory specialist based in Wellington where he is the director of the Medical Research Institute of New Zealand (MRINZ). Professor Beasley has provided commentary for each study featured in this Review.

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Salmeterol/fluticasone propionate (Seretide™) review of new indication data

Major recent studies on COPD and the safety and efficacy of SFC

The nature of small-airway obstruction in chronic obstructive pulmonary disease¹⁸

Authors: Hogg JC et al

Summary: Disease progression in COPD is associated with an accumulation of inflammatory mucous exudates in the lumen and infiltration of the wall by innate and adaptive inflammatory immune cells that form lymphoid follicles, together with a repair or remodeling process that thickens the walls of these airways.

Method: Surgically resected lung tissue specimens from 159 patients with COPD (39 in GOLD Stage 0, 39 in Stage 1, 22 in Stage 2, 16 in Stage 3, and 43 in Stage 4) were examined, to determine the evolution of the pathological effects of airway obstruction in patients with COPD.

Results: Strong associations were observed between COPD progression and increased volume of tissue in the airway wall ($p < 0.001$) and the accumulation of inflammatory mucous exudates in the small-airway lumen ($p < 0.001$). Inflammatory immune cells were measured in a subgroup of 40 patients; analyses revealed that as COPD progressed, there were significant increases in the percentage of airways with polymorphonuclear neutrophils, macrophages, CD4 cells, CD8 cells,

B cells, and with lymphoid follicles, as well as significant increases in the absolute volume of B cells and CD8 cells. According to multivariate analysis for all 159 patients and the subgroup of 40 patients, the strongest association with disease progression was an increase in the volume of the airway wall tissue.

Comment: This manuscript evaluated the relationship between the severity of COPD and the pathological findings in small airways. With increasing severity of COPD there was a progressive thickening of the airway wall and each of its compartments by a remodelling process. This increase in tissue is thought to contribute to both non-specific bronchial hyperresponsiveness, which is one of the best predictors of the rapid decline in FEV₁ in patients with COPD, and fixed airways obstruction, which is the physiological hallmark of COPD. The other main pathological finding was airways inflammation with the occlusion of smaller airways by inflammatory exudate, which once again was more marked in patients with more severe COPD. Both the innate and adaptive inflammatory immune responses are implicated in these pathological changes.

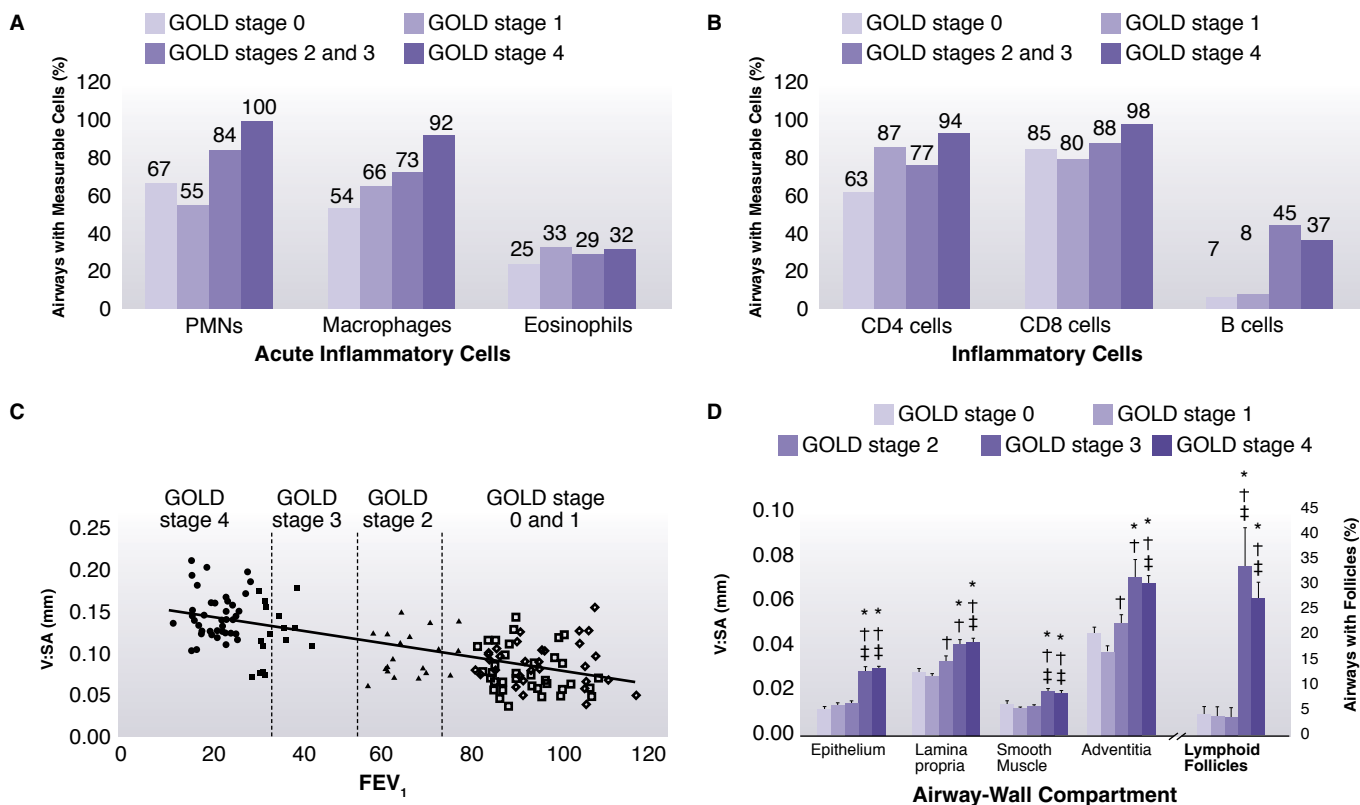


Figure 1: Clinical findings in patients with COPD according to the GOLD stage

Panel A shows the extent of the airway inflammatory response, as measured by the percentage of the airways containing polymorphonuclear neutrophils (PMNs), macrophages, and eosinophils, among patients in each GOLD stage of COPD. Panel B shows similar data for CD4 cells, CD8 cells, and B cells. Panel C shows the association between total wall thickness, measured as the ratio of the volume to the surface area (V:SA), and forced expiratory volume in one second (FEV₁) for all 159 patients. Panel D shows the mean (+SE) volume of epithelium, lamina propria, smooth muscle, and adventitial tissue expressed per unit of basement-membrane surface area (V:SA) and the percentage of airways that contained lymphoid follicles in all 159 patients. Patients with GOLD stages 2 and 3 have been combined in Panels A and B to make the number of patients similar in each group. Asterisks indicate $P < 0.001$ for the comparison with patients with GOLD stage 0. Daggers indicate $P < 0.001$ for the comparison with GOLD stage 1. Double daggers indicate $P < 0.001$ for the comparison with patients with GOLD Stage 2.

Salmeterol/fluticasone propionate (Seretide™) review of new indication data

Anti-inflammatory effects of salmeterol/fluticasone propionate in chronic obstructive lung disease¹⁹

Authors: Barnes NC et al

Summary: The treatment combination of SFC has broad spectrum anti-inflammatory effects in both current and former smokers with moderate to severe COPD.

Method: 140 current and former smokers with moderate to severe COPD were randomised to either SFC 50/500 µg twice daily or matching placebo for 13 weeks. Bronchial biopsies and induced sputum were obtained from all patients at baseline. Biopsies were repeated at 12 weeks and sputa at 8 and 13 weeks. Comparisons were made between active treatment and placebo for median change from baseline in the numbers of biopsy CD8 and CD68 cells/mm² and sputum neutrophils.

Results: The absolute number of biopsy CD8 cells was reduced from baseline by a significantly greater amount with SFC compared with placebo, resulting in a treatment difference of -117.9 cells/mm² (95% CI -208.6 to -41.9; p=0.015), a reduction of 36% over placebo (p=0.001). CD68 cells increased in number from baseline in both placebo and active treatment groups (see Figure 2). There was a progressive reduction in sputum differential (but not total) cell count with active treatment; the median between-treatment difference was significant at 13 weeks (-8.50%; 95% CI -15.25 to -1.75; p=0.037). Combination treatment was also associated with significant reductions in biopsy CD45 and CD4 cells, cells expressing genes for tumour necrosis factor-α and IFN-γ, and sputum total eosinophils. In addition, compared with placebo, SFC was associated with significantly greater improvements in lung function; at study end, the mean treatment difference was 173 ml for mean prebronchodilator FEV₁ (95% CI 104 to 242 ml; p<0.001) and 170 ml for forced vital capacity (FVC) (95% CI 41 to 299 ml; p=0.010).

Comment: Direct evidence that combination ICS/LABA therapy has broad anti-inflammatory effects in mild to moderately severe COPD. Importantly, combination therapy reduced sputum differential neutrophils and biopsy CD8+

cell counts, key parameters previously shown to relate to severity and disease progression in COPD. The nature and magnitude of the anti-inflammatory effects with combination therapy were significantly different from those previously observed with ICS alone. This observation is consistent with clinical data which have shown a greater efficacy of ICS/LABA compared with ICS therapy alone in COPD.

It is reasonable to assume that the anti-inflammatory effects contributed to the clinical efficacy demonstrated with combination ICS/LABA therapy in this study. The clinical effects were impressive – a 10% improvement in FEV₁ with 13 weeks of combination therapy compared with a 4% acute bronchodilator reversibility with salbutamol. It is likely that greater clinical benefit might be obtained with ICS/LABA therapy in subjects with COPD with greater acute bronchodilator reversibility.

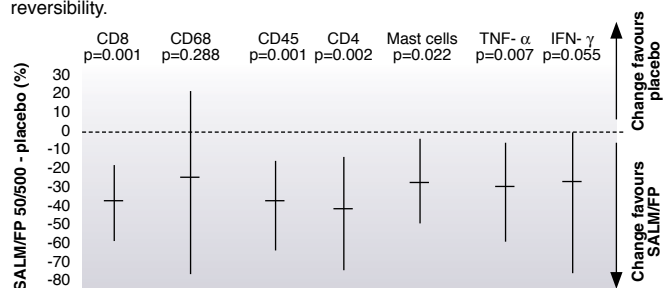


Figure 2. Median treatment differences in percentage change from baseline for biopsy endpoints. Hodges-Lehmann estimator of median treatment difference and 95% confidence interval presented. FP fluticasone propionate; SALM salmeterol.

Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease²⁰

Authors: Calverley PMA et al

Summary: In this study, SFC treatment was associated with a 17.5% reduction in the risk of dying from any cause over 3 years (p=0.052) compared to placebo. Combination treatment, when compared with placebo, also demonstrated a 25% (p<0.001) reduction in the rate of exacerbations, and significant improvements in health-related quality of life and FEV₁.

Method: 6184 patients with COPD were randomised to receive treatment with SFC 50/500 µg, or salmeterol 50 µg alone, fluticasone propionate 500 µg alone, or placebo, twice daily for 3 years. The primary outcome was the time to death from any cause for the comparison between the combination therapy group and the placebo group.

Results: Of a total of 6112 patients in the efficacy population, 875 deaths occurred within 3 years after randomisation. All-cause mortality rates at 3 years were 12.6% in the combination therapy group, 13.5% in the salmeterol-only group, 16.0% in the fluticasone propionate-only group, and 15.2% in the placebo group. The hazard ratio for death in the combination therapy group as compared with the placebo group was 0.825 (95% CI 0.681 to 1.002; p=0.052, adjusted for the interim analyses), corresponding to a reduction in the risk of death at any time in the 3 years of 17.5% (95% CI -0.2 to 31.9) (see Figure 3). Compared with placebo, combination therapy reduced the annual rate of exacerbations from 1.13 to 0.85 and improved health status and lung function.

The probability of having pneumonia reported as an adverse event was significantly greater among patients receiving medications containing fluticasone propionate (19.6% in the combination therapy group and 18.3% in the fluticasone propionate group) than in the placebo group (12.3%) and the salmeterol group (13.3%, p<0.001 for all comparisons between both the combination therapy and fluticasone groups and the placebo group).

Comment: The interpretation of the TORCH study has been dominated by consideration of the 17.5% reduction in mortality associated with SFC compared with placebo therapy. This difference was not statistically significant, with a P value of 0.052. In contrast, there was clear evidence of greater benefit with SFC in terms of a statistically significant reduction in exacerbations, including those

exacerbations requiring hospital admission, and improved health status and lung function. To get an idea of the magnitude of the benefit it has been calculated that the number needed to treat to prevent an exacerbation in one year was 4, and the number needed to treat to prevent a hospital admission was 32.

It is important to recognise that most clinical trials of SFC, including the TORCH study, have used a high dose of fluticasone at 1000µg per day via discus. However, the dose-response relationship of ICS in COPD has yet to be established and if similar to that for asthma, it is likely that 1000µg per day of fluticasone is greater than that required to obtain maximum efficacy in most patients. It is essential that the dose-response relationship of ICS in COPD is established and that lower dose combinations are trialled to determine whether they may have a different efficacy/side effect profile.

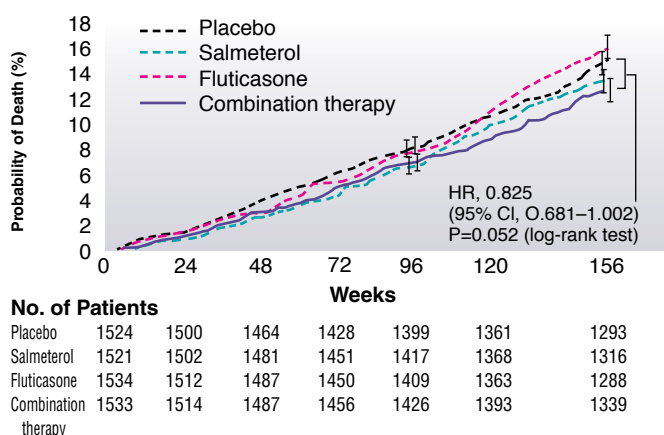


Figure 3: Deaths from any cause

Salmeterol/fluticasone propionate (Seretide™) review of new indication data

Tiotropium in combination with placebo, salmeterol, or fluticasone-salmeterol for treatment of chronic obstructive pulmonary disease: a randomized trial²¹

Authors: Aaron SD et al

Summary: The addition of SFC to tiotropium therapy did not statistically influence rates of chronic obstructive pulmonary disease (COPD) exacerbation in patients with moderate to severe COPD but did improve lung function, quality of life, and hospitalisation rates in these patients.

Method: This multicentre trial involved 449 patients with moderate to severe COPD; inclusion criteria were ≥ 1 exacerbation requiring treatment with systemic steroids or antibiotics within 12 months before randomisation, age older than 35 years, ≥ 10 pack-years of cigarette smoking, $FEV_1:FVC < 0.70$, and postbronchodilator FEV_1 less than 65% predicted.

Patients were randomised to 1 year of treatment with tiotropium (18 μg once daily) plus placebo inhaler ($n=156$); tiotropium plus salmeterol (25 $\mu\text{g}/\text{puff}$, 2 puffs twice daily; $n=148$), or tiotropium plus SFC (250/25 $\mu\text{g}/\text{puff}$, 2 puffs twice daily; $n=145$). The main outcome measure was the proportion of patients who had a COPD exacerbation within 1 year of randomisation requiring treatment with systemic steroids or antibiotics.

Results: The proportion of patients who had a COPD exacerbation was 62.8% in the tiotropium plus placebo group, 64.8% in the tiotropium plus salmeterol group (difference, -2.0% ; 95% CI, -12.8% to 8.8%), and 60.0% in the tiotropium plus SFC group (difference, 2.8% ; 95% CI, -8.2% to 13.8%). Although these differences were not statistically significant, sensitivity analyses showed that the point estimates and 95% confidence

bounds favoured tiotropium plus salmeterol and tiotropium plus SFC (see Table 2).

Compared with tiotropium plus placebo, tiotropium plus SFC was associated with improved lung function (FEV_1 ; $p=0.049$) and disease-specific quality of life on the St. George's Respiratory Questionnaire ($p=0.01$), as well as fewer hospitalisations for COPD exacerbation (incidence rate ratio [RR], 0.53; 95% CI, 0.33 to 0.86) and fewer all-cause hospitalisations (RR, 0.67; 95% CI, 0.45 to 0.99). In contrast, tiotropium plus salmeterol did not statistically significantly improve lung function or hospitalisation rates compared with tiotropium plus placebo.

Comment: This study answers the clinical question: which is the preferred therapeutic response in a patient with moderate to severe COPD not adequately controlled on regular tiotropium therapy – the addition of a LABA or ICS/LABA therapy? The findings clearly show that the preferred option is to add ICS/LABA therapy, an approach which would be expected to improve quality of life and lung function, and to reduce severe exacerbations resulting in hospital admission. The benefits obtained were of clinical significance, for example, the 50% reduction in hospitalisations for COPD exacerbations, the one-third reduction in all-cause hospitalisations and reduction of four points in the SGRQ health-related quality of life score. The finding that adding ICS/LABA to tiotropium did not affect overall exacerbation rates while reducing hospital admissions suggests that ICS/LABA therapy may modify the severity rather than the frequency of exacerbations. In contrast, there is no substantive clinical benefit in adding LABA monotherapy to tiotropium.

Table 2. Exacerbations of COPD during 1 year

Outcome	Tiotropium + Placebo (n=156)	Tiotropium + Salmeterol (n=148)	Tiotropium + SFC (n=145)
Primary analysis[†]			
Patients with ≥ 1 acute exacerbation of COPD, <i>n</i> (%)	98 (62.8)	96 (64.8)	87 (60.0)
Absolute RR compared with tiotropium + placebo (95% CI), <i>percentage points</i>		-2.0 (-12.8 to 8.8)	2.8 (-8.2 to 13.8)
Sensitivity analysis 1[‡]			
Patients with ≥ 1 acute exacerbation of COPD, <i>n</i> (%)	117 (75.0)	107 (72.3)	96 (66.2)
Absolute RR compared with tiotropium + placebo (95% CI), <i>percentage points</i>		2.7 (-7.2 to 12.6)	8.8 (-1.5 to 19.0)
Sensitivity analysis 2[§]			
Patients with ≥ 1 acute exacerbation of COPD, <i>n</i> (%)	112 (71.8)	104 (70.3)	93 (64.1)
Absolute RR compared with tiotropium + placebo (95% CI), <i>percentage points</i>		1.5 (-8.7 to 11.7)	7.6 (-2.9 to 18.1)
Exacerbations of COPD			
All exacerbations, <i>n</i>	222	226	188
Duration of follow-up, <i>patient-years</i>	138.0	129.4	137.1
Mean exacerbations per patient-year, <i>n</i>	1.61	1.75	1.37
Incidence rate ratio compared with tiotropium + placebo (95% CI)	–	1.09 (0.84 to 1.40)	0.85 (0.65 to 1.11)

COPD = chronic obstructive pulmonary disease; SFC = salmeterol/fluticasone propionate; RR = risk reduction.

[†] Assuming that all patients who were lost to follow-up did not have an exacerbation.

[‡] Assuming that all patients who were lost to follow-up had an exacerbation.

[§] Assuming that all patients who were lost to follow-up had exacerbations at the same time as those who continued in the study.

^{||} Accounting for between-patient variability.

Salmeterol/fluticasone propionate (Seretide™) review of new indication data

The prevention of COPD exacerbations by salmeterol/fluticasone propionate or tiotropium bromide²²

Authors: Wedzicha JA et al

Summary: Patients with moderate-severe COPD treated with SFC experienced a similar rate of exacerbations to patients treated with tiotropium, but achieved statistically significant improvements in health status and greater survival benefit.

Method: 1323 patients with moderate-severe COPD were randomised to SFC 50/500 µg twice daily or tiotropium bromide 18 µg once daily, for 2 years. The primary efficacy endpoint was the rate of healthcare utilisation exacerbations (defined as those requiring treatment with oral corticosteroids and/or antibiotics or requiring hospitalisation).

Results: Tiotropium treatment was associated with a 29% higher probability of study withdrawal prior to week 104 than SFC. During the study period, 62% of the combination therapy group and 59% of the tiotropium group had ≥1 exacerbation requiring therapeutic intervention. The estimated annual exacerbation rate was 1.28 in the combination therapy group and 1.32 in the tiotropium group (rate ratio 0.967 [95% CI 0.836 to 1.119]; p=0.656). At week 104, the St. George's Respiratory Questionnaire total score was statistically significantly lower in the combination therapy group versus the tiotropium group (difference 2.1 units, 95% CI 0.1 to 4.0; p=0.038). Mortality was significantly lower in the combination therapy group; 21 (3%) of patients in this group died compared to 38 (6%) in the tiotropium group (p=0.032). Pneumonia was diagnosed during study treatment in 8% of combination therapy recipients and 4% of tiotropium recipients (p=0.008).

Comment: This is the first large scale trial which has compared the efficacy and safety of tiotropium with that of combination SFC treatment in severe COPD. The strengths of the trial include its size, long duration and the inclusion of patients with severe COPD. On balance, combination SFC therapy resulted in greater clinical benefit. Although both treatments reduced exacerbation frequency by a similar magnitude, SFC treatment was associated with better health status, fewer patient withdrawals and a lower mortality rate than tiotropium. The 40% reduction in mortality with SFC was striking, and was primarily due to a reduction in deaths

from cardiac disorders and cancers. SFC use was associated with an increased risk of pneumonia, an association which has been noted previously and is presumably due to the ICS component.

Another observation was that there were few exacerbations requiring oral corticosteroid treatment in the SFC group compared with tiotropium, but relatively more patients treated with antibiotics. This can be interpreted as providing indirect evidence that the clinical benefits with these agents are achieved through different biological mechanisms. It also provides a rational basis for treating patients with COPD with both SFC and tiotropium, an approach which leads to greater efficacy than either alone.

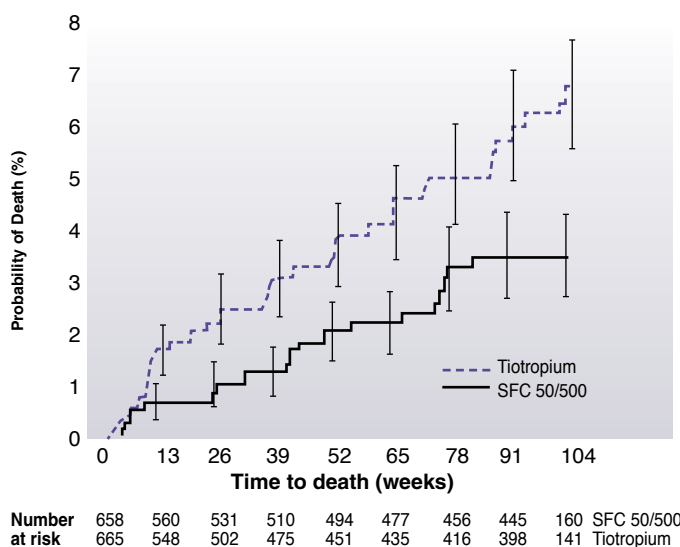


Figure 4: Time to death on treatment in the SFC and tiotropium treatment groups

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