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REVIEW

A Review of Salmeterol–Fluticasone Propionate in Combination: Its Use in the Treatment of Chronic Obstructive Pulmonary Disease

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Abstract: Tiotropium bromide (TIO), a long-acting anticholinergic bronchodilator, is now used world-wide for the treatment of Chronic Obstructive Pulmonary Disease (COPD). However, the GOLD guidelines recommend another, or additional medication for symptomatic patients with GOLD stage III or IV disease, forced expiratory volume in 1 second (FEV_1) less than 50% of the predicted value, and repeated exacerbations. Several lines of evidence such as the TRISTAN study have shown the synergistic effects of a salmeterol–fluticasone propionate combination (SFC), with significant improvements of pulmonary function, health status, exacerbation rates, and quality of life in patients with COPD, compared with using individual components of SFC. But they didn't obtain any improvement in the data for mortality, which is our major clinical concern. The TORCH study is a major study which investigated all-cause mortality rates, but it showed no significant difference of mortality among SFC, individual drugs and placebo groups. The INSPIRE study showed significant improvement of mortality in the SFC treatment group, compared with the TIO. However, the higher incidence of pneumonia in the SFC group remains a subject of debate. Some studies showed that SFC therapy has lower medical costs with good patient compliance, which may become a reason for choosing the therapy.
The new 2010 NICE GOLD Guideline recommends the "triple" therapy with SFC and TIO, when the FEV_1% predicted is less than 50% in the presence of persistent exacerbations or breathlessness. The advantages of "triple" therapy may outweigh the disadvantages of each medication. This review focuses upon the therapeutic potential of SFC for the treatment of COPD.

Keywords: salmeterol–fluticasone propionate combination (SFC), chronic obstructive pulmonary disease (COPD), tiotropium bromide (TIO)

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Introduction

Chronic obstructive pulmonary disease (COPD) is a major cause of chronic morbidity and mortality worldwide. COPD was ranked tenth as a cause of disability-adjusted life years lost worldwide in 1990,[1] and the World Health Organization (WHO) previously reported that COPD might become the third leading cause by 2020.[2] Nevertheless, COPD is now listed as the third leading cause of death in advance of 2020. In this situation, we must do our utmost to stop further increases in COPD deaths. COPD is characterized by a slowly progressive airway limitation that is not fully reversible. The airway limitation is associated with an abnormal inflammatory response of the lungs caused by cigarette smoking, chronic exposure to environmental pollutants, and, occasionally, genetic deficiency such as alfa1-antitrypsin.[3] Susceptibility to developing COPD with smoking or other environmental factors may depend on the concomitant presence of several gene polymorphisms that act together.[4] If irreversible pulmonary structural damage has already progressed, usually when patients with COPD complain of clinical symptoms such as dyspnea on effort, and the diagnosis is made, it is difficult to treat the disease. Another reason for the difficulty in treating COPD is that there are no efficacious therapeutic methods which impact its pathogenesis. Although the accurate pathogenic mechanisms have been under debate, the proteinase versus anti-proteinase imbalance remains a major hypothesis of the pathogenic determinants of COPD.[5] Considering the significant contributions of neutrophil-derived proteases including human neutrophil elastase and matrix metalloproteinases as terminal tissue destroyers, medications against excessive levels of these proteinases are currently being developed, but few clinical trials have been conducted.[6,7] Exacerbations accelerate the decline in pulmonary function and worsen health status and quality of life for patients with COPD, which significantly worsens the severe morbidity and mortality of this disease. Therefore, the prevention of exacerbations may be pivotal in the treatment of COPD in present clinical practice. In 2001, the global initiative for chronic obstructive lung diseases (GOLD) was first launched in collaboration with the WHO and the National Heart, Lung and Blood Institute, USA (NHLBI) to prevent disease progression and exacerbations, relieve symptoms and improve health status. From the first version to the current the 2010 UK National Institute for Health and Clinical Excellence (NICE) GOLD Guideline, the GOLD guidelines recommend comprehensive management of COPD which includes proper assessment, disease monitoring, reduction of risk factors, drug treatments and pulmonary rehabilitation.[8,9] The importance of smoking cessation and control of environmental indoor and outdoor pollutants are primarily emphasized to avoid risk factors. Although pharmacologic therapy is one part of COPD management, short- or long-acting bronchodilators are effective for reducing the work of breathing and alleviating dyspnea. Furthermore, the GOLD guidelines recommend additional treatment with inhaled corticosteroids (ICS) for symptomatic patients with GOLD stage III or IV disease, forced expiratory volume in 1 second (FEV_1) $< 50\%$ of the predicted value, and repeated exacerbations.[8,9] ICS has been established as a first-line, gold standard for the treatment of asthma of all severities. The synergistic effects of combination therapy with ICS and long-acting beta-adrenergic agonists (LABA) are also well-known in asthma therapy.[10] Fluticasone propionate (FP) 100 µg and salmeterol 50 µg combined in the Diskus® powder delivery device offered significant improvement of lung function in patients with asthma over FP or salmeterol alone at the same doses.[11–13] It may be inappropriate for us to adapt the same synergistic effect of ICS and LABA combination in the treatment of COPD as bronchial asthma. However, based on these observations, we anticipated the similar synergistic effects with the combination of LABA and ICS in COPD therapy. This review focuses on the efficacy of salmeterol–FP combination (SFC), the Diskus® inhaler, in the treatment of COPD.

Mechanism of Action Profile of SFC in COPD

There is evidence showing the synergistic effects of co-administration of FP and salmeterol at the molecular level. Corticosteroids bind to cytoplasmic glucocorticoid receptors (GRs), which then translocate to the nucleus where they regulate gene expression. Salmeterol enhanced FP effects on GR nuclear translocation in epithelial and macrophage-like airway cell lines.[14] Furthermore, salmeterol in combination with FP enhanced glucocorticoid response element-luciferase reporter gene activity and mitogen-activated

protein kinase phosphatase 1 (MKP-1) and secretory leuko-proteinase inhibitor (SLPI) gene induction, thereby enhancing the ainti-infalammatory effects of FP.[14] In contrast, FP enhances the beta-agonist effects of salmeterol.[15] Glucocorticoids prevent homologous down-regulation of beta 2-receptor number and mRNA expression at the transcriptional level by activating the transcription factor, cyclic AMP response element binding protein, without affecting beta 1-receptors.[15]

Airway inflammation in COPD is characterized by infiltration of CD8+ T cells and CD68+ macrophages and an increased number of neutrophils. SFC reduced by 36% the numbers of bronchial biopsy CD8+ T cells as compared with a placebo and significantly reduced CD45+ and CD4+ cells in biopsy specimens and cells expressing genes for tumor necrosis factor-alpha and IFN-gamma and sputum total eosinophils (all $P < \text{or} = 0.03$).[16] Another randomized controlled study showed that SFC significantly reduced CD8+ T cells and CD68+ macrophages in bronchial biopsies, but such a marked effect was not seen with FP alone.[17]

Considering the pathogenic contributions of neutrophil-derived proteases including neutrophil elastase and matrix metalloproteinases, preventing proteinase excess may be a highly effective therapeutic approach. However, as mentioned above, there have been no developments in medications which directly impact on the pathogenesis of COPD.

Neutrophils are recruited into airway tissues by various chemical mediators and cytokines such as interleukin (IL)-8, a major neutrophil chemoattractant.[18] IL-8, a CXC chemokine, has a potent profile in the enhancement of neutrophil chemotaxis, the positive release of proteolytic enzymes contained in azurophilic granules, and the expression of neutrophil surface adhesion molecules.[19,20] IL-8 levels are elevated in bronchoalveolar lavage fluid from patients with COPD.[21] IL-8 levels in induced sputum are also associated with the extent of neutrophilic inflammation and the severity of COPD.[22] Cigarette smoke is the major risk factor for the development of COPD. Cigarette smoke induces increased expression of CXC receptors and the production of reactive oxygen species that may explain the strong production of IL-8 by neutrophils and macrophages. A previous in vitro study showed that SFC had an additive suppressive effect on the cigarette smoke-induced production of IL-8 by human neutrophils, which was explained by increased mRNA expression of MAP kinase phosphatase-1, the glucocorticoid receptor and increased glucocorticoid receptor translocation to the nuclei of neutrophils.[23] Another in vitro study showed that SFC inhibited cigarette smoke-induced IL-8 production.[24] Human airway smooth-muscle cells, also a rich source of IL-8, and tumor necrosis factor (TNF)-alpha, strongly enhance IL-8 release from airway smooth-muscle cells in a time- and concentration-dependent manner. This indicates that IL-8 is potentially a therapeutic target in COPD treatment. SFC significantly inhibited TNF-alpha-induced IL-8 release from human airway smooth-muscle cells, as compared with FP alone.[25] The above findings suggest the hypothesis that the synergistic interactions of SFC against IL-8 release may prevent the progression of COPD, a neutrophil-dominant lung disorder.

Surfactant protein D (SP-D) is mainly produced and secreted by alveolar type II pneumocytes. As serum levels of SP-D increase with lung injury, SP-D may become a good biomarker for COPD showing the peripheral airway damage near alveoli.[26] Serum SP-D levels were significantly increased in patients who experienced an acute exacerbation as compared to those with stable disease or control subjects, suggesting SP-D to be a potential diagnostic biomarker for COPD exacerbations.[27] A double-blind randomized placebo-controlled trial involving 11 centers showed circulating SP-D levels to be significantly reduced in the FP or SFC treatment groups as compared with the placebo.[28] These observations suggest the hypothesis that circulating SP-D levels may become a marker for improving the damage in COPD in response to treatment with SFC. However, the benefits at the molecular level are still unclear and the accurate mechanism concerning the synergistic effects of co-administration of FP and salmeterol is now under debate.

Clinical Studies

Comparison of clinical efficacies between SFC and individual agents

There are several studies concerning the comparison of clinical efficacies between SFC and individual drugs. The salmeterol 50 µg/FP 250 µg combination (SFC 50/250) administered regularly via a Diskus® inhaler for a 52-week period significantly improved

respiratory functions such as FEV_1 and morning peak expiratory flow (PEF), as well as symptom scores in patients with moderate COPD previously treated with theophylline, as compared with salmeterol alone or a placebo.[29] Another randomized, double-blind, parallel-group, multicenter study compared the effects of SFC 50/250 and salmeterol 50 μg twice-daily on moderate/severe exacerbations.[30] In this study, 782 patients with COPD received standardized treatment with SFC 50/250 during a 1-month run-in, followed by randomization to SFC 50/250 or salmeterol for 12 months. SFC 50/250 significantly reduced the annual rate of moderate to severe exacerbations, by 30.5% as compared with salmeterol ($P < 0.001$), the risk time to first exacerbation by 25% ($P = 0.003$) and the annual rate of exacerbations requiring oral corticosteroids by 40% ($P < 0.001$). Statistically significant reductions in albuterol use, dyspnea scores, and nighttime awakenings and numerical benefits on quality of life were also seen with SFC as compared with salmeterol. Another randomized, double-blind, multicenter, placebo-controlled study at 76 investigative sites in the United States was conducted for 24 weeks in 723 patients with COPD (a mean baseline FEV_1 of 42% of the predicted value).[31] The morning pre-dose values of FEV_1 in the SFC 50/250 treatment group were significantly increased as compared with the salmeterol alone or placebo groups. The 2-h post-dose FEV_1 values in the SFC 50/250 treatment group were also significantly increased as compared with the FP alone or placebo groups. The TRial of Inhaled STeroids ANd long-acting beta2 agonists study (TRISTAN study), a randomized, double-blind, multicenter, parallel-group, placebo-controlled study, was conducted in 1465 outpatients with COPD in 25 countries in 2003. After 12 months of treatment, the salmeterol 50 μg/FP 500 μg (SFC 50/500) combination therapy improved pretreatment FEV_1 significantly more than did the placebo ($P < 0.0001$), salmeterol alone ($P < 0.0001$), or FP alone ($P < 0.0001$). SFC also significantly improved health status and produced the greatest reduction in daily symptoms for 12 months, with no greater risk of side-effects than with use of either component alone.[32] Another randomized, double-blind, parallel-group study by O'Donnell et al demonstrated that SFC decreases lung hyperinflation at rest and during exercise with an associated increase in exercise endurance time, together with improvements in pulmonary function values, as compared with the placebo.[33] However, although all the above studies showed the comparative effects of SFC concerning respiratory functions, symptom scores and quality of life, they did not obtain improvement of mortality which is our major clinical concern.

The Towards a Revolution in COPD Health (TORCH) study is one of the major studies which investigated all-cause mortality rates, together with the frequency of exacerbations, health status and spirometric values, among the SFC, salmeterol alone, FP alone and placebo groups.[34] This randomized double-blind trial was conducted at 444 centers in 42 countries for a period of 3 years. The annual rate of exacerbations was significantly reduced from 1.13 to 0.85 in the SFC group, and health status and spirometric values also improved significantly ($P < 0.001$ for all comparisons with placebo). The hazard ratio for death in the SFC 50/500 group was 0.825 (95% confidence interval 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% as compared with the placebo group. However, all-cause mortality rates did not differ significantly among the SFC 50/500, salmeterol alone, FP alone and placebo groups (12.6%, 13.5%, 16.0% and 15.2%, respectively). No significant impact on mortality was found even with additional information from the TORCH trial. Along with the results of the TORCH study, the Cochrane Database suggested the requirement of additional investigation of the superiority of combination inhalers concerning mortality rates.[35] The database also suggested that the SFC should be viewed against the increased risk of side-effects, particularly pneumonia. These results also piqued our interest in the comparative effects of SFC versus anticholinergic agents, another major pharmacologic management tool.

Comparison of clinical efficacies between SFC and anticholinergic agents

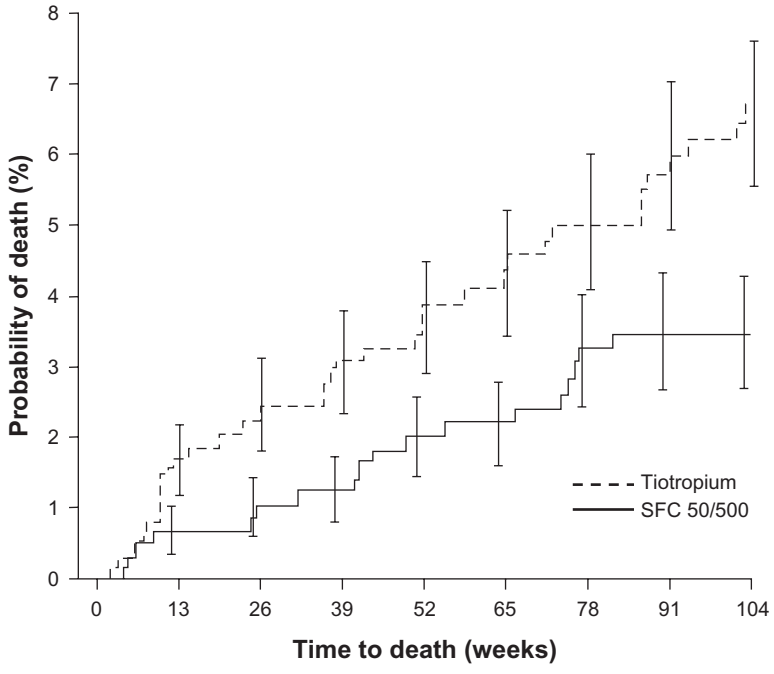
This review picks up two major studies concerning the comparison of clinical efficacies between SFC and anticholinergic agents; one is versus ipratropium bromide/albuterol, and another is versus tiotropium bromide. Donohue et al evaluated the comparison between SFC 50/250 twice daily via the Diskus® inhaler and

ipratropium bromide/albuterol 36/206 µg four times daily via a metered-dose inhaler over 8 weeks.[36] This randomized, double-blind, double-dummy, parallel group, and multicenter study was conducted in 365 patients with symptomatic COPD at 41 research sites in the US. SFC was more effective than ipratropium bromide/albuterol for improving morning pre-dose FEV_1, morning PEF, 6-hour FEV_1 area under the curve, the Transition Dyspnea Index focal score, daytime symptom score, night-time awakenings, sleep symptoms and albuterol-free nights.

The Investigating New Standard for Prophylaxis in Reducing Exacerbations (INSPIRE) study investigated the comparative effects between SFC 50/500 twice daily and tiotropium bromide (TIO) 18 µg once daily. This 2-year, randomized, double-blind, and double-dummy parallel study was conducted in 1323 patients with severe and very severe COPD with the aim of preventing exacerbations and related outcomes.[37] Although there was no statistically significant difference in hospital admission rates due to exacerbations between the SFC and TIO treatment groups (1.28 and 1.32 events/patient during the 2 years, respectively), St. George's Respiratory Questionnaire score and mortality were significantly lower in the SFC than in the TIO group (Fig. 1). Exacerbations requiring treatment with oral corticosteroids were less frequent in patients on SFC. Mortality was significantly lower in the SFC group; 21 (3%) patients died versus 38 (6%) in the TIO group ($P = 0.032$).[37] The incidence of pneumonia was significantly higher in the SFC (8%) than in the TIO group (4%).[37] Conversely, although there were also more cases of pneumonia in patients on SFC than in those on TIO, exacerbations requiring treatment with antibiotics were more frequent in patients treated with SFC. The INSPIRE study is a well-known comparative study which evalauted the mortality between SFC and TIO, and the relative benefits and harms of each have yet to be fully elucidated.[38]

Advantages of "triple" therapy with salmeterol/FP and TIO

The combination of SFC and TIO is actually used in daily clinical practice. The new 2010 NICE GOLD Guideline also recommends the "triple" therapy such



The hazard ratio for SFC versus tiotropium was 0.48 (95% CI, 0.27–0.85; $P = 0.012$)

Figure 1. Time to death on SFC and tiotropium treatment groups.
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as the combination of SFC and TIO, when the FEV_1% predicted is <50%, in the presence of persistent exacerbations or breathlessness.[9] A randomized, double blind, double dummy, three-way cross-over study by Singh et al demonstrated that SFC50/500+TIO significantly improved spirometry parameters, such as FEV_1 and inspiratory capacity, at 14 days, as compared with TIO alone or SFC alone. The post-dose specific airways conductance area under the curve in plethysmography was also significantly higher on day 14 after SFC+TIO than with TIO (22%) or SFC alone.[39] A randomized, double-blind, placebo-controlled trial by Aaron et al showed that SFC+TIO significantly improved lung function, quality of life and hospitalization rates for COPD exacerbation in patients with moderate to severe COPD as compared with TIO + placebo, while TIO + salmeterol did not significantly improve lung function or hospitalization rates as compared with TIO + placebo.[40] Another randomized study in patients with severe-to-very severe stable COPD also showed that pulmonary functions, including trough FEV_1, significantly improved over 3-month treatment periods in the SFC 50/500+TIO as compared with the SFC alone or TIO alone group (Fig. 2).[41] These studies suggested a synergic effect of salmeterol and FP when combined with TIO, which was not obtained by additional treatment with salmeterol alone.

Safety and Adverse Effects

Treatment with SFC is generally well tolerated in almost all clinical studies. However, the incidence

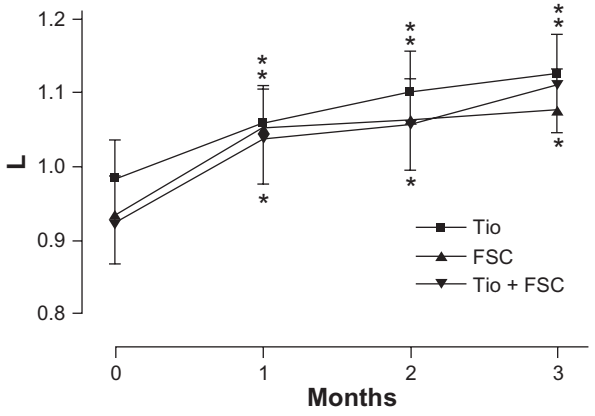

Figure 2. Mean FEV_1 values during 3 months of therapy with fluticasone propionate 500 μg/salmeterol 50 μg twice daily, tiotropium 18 μg once daily, and their combination, in patients suffering from severe to very severe COPD.
Reprinted with permission from Elsevier.[41]

of pneumonia is among the most important clinical concerns in SFC treatment of COPD. In a previous randomized, double-blind, parallel-group, multicenter study by Ferguson et al pneumonia was reportedly more frequent with SFC 50/250 than with salmeterol (7% vs. 2%).[30] As noted above, according to the TORCH study, the incidence of pneumonia was significantly higher in the SFC than in the other groups: (19.6%, 18.3%, 13.3% and 12.3% in the SFC 50/250, FP alone, salmeterol alone and placebo groups, respectively (all $P < 0.001$)).[34] However, there was no corresponding increase in pneumonia-related hospitalizations or deaths in the SFC group. The decrease in the exacerbation rate (–0.28 events/100 patients/year) was greater than the increase in pneumonia (+0.03 events/100 patients/year). A more recent post-hoc analysis of TORCH data revealed 88 pneumonia events per 1000 treatment-years for SFC 50/500 and 84 events per 1000 treatment-years for FP, versus 52 events per 1000 treatment-years with salmeterol or placebo. The INSPIRE study, a trial examining the effects of SFC 50/500 versus TIO on exacerbation rates, found equivalent exacerbation outcomes, but a higher pneumonia incidence in the SFC group (8% vs. 4%; $P < 0.01$).[37] However, there was still a mortality reduction in favor of the ICS-treated group. A recent study by Molina et al found outpatient therapy with ICS to be associated with significantly lower 30- and 60-day mortalities in hospitalized COPD patients with pneumonia.[42] The 2010 NICE GOLD Guideline concludes that, as there is a small increased risk of non-fatal pneumonia with ICS usage, patients should be warned about this.[9] SFC 50/250 twice daily improved morning lung function over 24 weeks as compared with FP or salmeterol treatment alone in patients with COPD, with no additional safety concerns for the combination treatment.[31] Adverse events occurred in 9%, 11%, 15%, and 20%, respectively, of patients in the placebo, salmeterol, FP and SFC 50/250 groups. Drug-related adverse events that occurred at a frequency of ≥4% in any one treatment group were throat irritation, hoarseness/dysphonia, headaches and candidiasis of the mouth and throat (incidence of candidiasis: placebo group, <1%; salmeterol group, 3%; FP group, 6%; and SFC 50/250 group, 9%). The number of patients who experienced adverse events resulting in withdrawal from the study was similar across treatment groups (range, 4% to 5%).

No deaths occurred, and the incidences of serious adverse events were low and similar across treatment groups (placebo group, 6%; SM group, 3%; FP group, 5%; SFC 50/250 group, 4%). There were no clinically significant ECG abnormalities in the SFC 50/250 group. In three randomized, double-blind, 24-week or 52-week studies in more than 2850 patients with COPD, administration of SFC twice daily provided greater improvement in lung function than placebo or either component alone at the same nominal dosage.[43] However, candidiasis, hoarseness/dysphonia, throat irritation and headache occurred more frequently with SFC than with placebo in COPD patients. One of the most frequent adverse events associated with ICS use is oral candidiasis. Donohue et al also reported that, although the incidence of adverse events was similar between SFC 50/250 and ipratropium bromide/albuterol groups, the incidence of oral candidiasis was higher in the SFC group.[36]

Besides the traditional characterization of airflow obstruction, COPD is associated with significant systemic abnormalities, such as renal and hormonal abnormalities, malnutrition, muscle wasting, and osteoporosis. Therefore, we medical doctors should consider the risk of onset of systemic adverse effects such as diabetes and osteoporosis. In their large cohort study included 388,584 patients, Suissa et al recently showed that current use of ICSs was associated with a 34% increase in the rate of diabetes (rate ratio [RR] 1.34; 95% confidence interval [CI], 1.29–1.39) and in the rate of diabetes progression (RR 1.34; 95% CI, 1.17–1.53).[44] The risk increases were greatest with the highest inhaled corticosteroid doses, equivalent to fluticasone 1000 μg per day or more (RR 1.64; 95% CI, 1.52–1.76 and RR 1.54; 95% CI, 1.18–2.02; respectively). They concluded that the risks are more pronounced at the higher doses currently prescribed in the treatment of COPD.

Osteoporosis is one of the systemic features of COPD and is also another well-known adverse effect of corticosteroids. ICSs are associated with both increased bone loss and fracture risk. This might be a result of confounding by disease severity, but high doses of ICS have similar effects as equipotent doses of oral corticosteroids.[45] In case of SFC usage, the post hoc safety analysis of TORCH study data showed that there were no significant differences in bone density between the SFC and placebo groups.[34]

There are two types of SFC commercially available worldwide: SFC hydrofluoroalkane 134a Metered-Dose-Inhaler (MDI) and SFC dry powder in a Diskus® inhaler. Koser et al compared efficacy and safety between SFC MDI and SFC 50/250 Diskus® in a multicenter, randomized, double-blind, 12-week study.[46] Lung functions including FEV_1 and PEF, and albuterol use were similar for the two formulations. The most common adverse events during treatment were headache (8% and 6% of patients), nasopharyngitis (4% and 6%), cough (3% and 4%) and sinusitis (2% and 5%) for SFC MDI and SFC Diskus® inhaler, respectively. Pneumonia was recorded as an adverse event in 2 (2%) patients in the SFC Diskus® arm.

Patient Drug Compliance

Treatment acceptance and compliance with treatment are among the most important factors in inhalation therapy. However, treatment continuation is generally low for all inhaled medications as compared with post oral medications. A previous study showed low treatment continuation with ICS in the Netherlands where only 18% of all patients continued on the treatment for one year.[47] Another previous study concerning treatment continuation and compliance with all inhaled medications for COPD including TIO and SFC was conducted in 31,368 patients.[48] In that study, other than patients taking the TIO (almost 50% for 12 months), those taking SFC showed the next highest continuation rate among the other drugs with an almost 30% continuation rate for 12 months. Poor compliance is often caused by improper use of an inhaled device with poor inhaler technique, which may lead to exacerbations in COPD and mortality. A recent randomized double-blind trial comparing inhaled.

SFC 50/500 twice daily with placebo showed that drug compliance with inhaled medication was significantly associated with reduced risk of death and hospitalization due to exacerbations in COPD.[49] The proper choice of inhaled device may become an important therapeutic factor enhancing and maintaining patient acceptance and compliance with the inhaled medication. In our previous study, the Diskus® device showed high patient acceptance and compliance.[50] Patients who were prescribed SFC also obtained more refills than those prescribed salmeterol or ICS.[51] Medical cost is another important factor

in the continuation of inhaled drugs requiring high compliance with treatment. Comparing the initial health care costs during the first 12 months of follow-up, total COPD-related cost was lower with SFC than other medications such as salmeterol alone, ICS alone, ipratropium alone, or the ipratropium/albuterol combination.[52] Patient compliance, as measured by medication possession ratio, was 12% greater with SFC than ipratropium ($P < 0.05$). The combination SFC therapy depends on the availability of single inhaler devices that contain both medications, and lower medical costs also enhance both health status and patient compliance.

Conclusion

Tiotropium bromide (TIO) is now a major drug used world-wide for the treatment of COPD. Under this situation, this review showed the therapeutic potentiality of SFC in COPD therapy. As recommended in the GOLD guidelines, additional medications are required for symptomatic patients with GOLD stage III or IV disease, forced expiratory volume in 1 second (FEV_1) less than 50% of the predicted value, and repeated exacerbations. However, many studies including TRISTAN study showed that, SFC alone, but not together with TIO, enabled significant improvement of pulmonary function, health status and daily symptoms as compared with individual components of SFC. Those results suggested that SFC showed sufficient therapeutic potentiality, which prompted us to make a therapeutic comparison between SFC and TIO. The INSPIRE study showed that, despite there being no statistically significant differences between the groups, the 1.28 fold increase in the number of hospital admissions during 2 years due to exacerbations in the SFC group was lower than the 1.32 fold increase in the TIO group. Considering the disease severity of patients at entry in the INSPIRE study, whose average FEV_1 values were almost 39%, the exacerbation rates in the SFC group were sufficiently lowered as were those in the TIO treatment group. However, the incidence of pneumonia was significantly higher in the SFC (8%) than in the TIO group (4%) in the INSPIRE study. As the increased occurrence of airway infection is possibly influenced by ICS, further investigation is required. Considering the balance between therapeutic benefits and adverse effects, we have to take into account the small increased risk of non-fatal pneumonia.

Our major clinical concern in COPD therapy is the improvement of mortality. The TORCH study showed a significant reduction of the annual rate of exacerbations in the SFC group, but all-cause mortality rates did not differ significantly among the SFC, salmeterol and FP alone groups. The INSPIRE study showed a significantly lower mortality in the SFC group (3%) than in the TIO group (6%) ($P = 0.032$). However, the beneficial reduction in COPD mortality suggests that SFC is a promising candidate for the treatment of COPD despite the increased incidence of pneumonia.

This review shed light on the advantages of "triple" therapy with SFC and TIO. As recommended in the new 2010 NICE GOLD Guideline, the "triple" therapy is actually useful when the FEV_1% predicted is $<50\%$ in the presence of persistent exacerbations or breathlessness. Several clinical studies showed that SFC+TIO significantly improved lung function and quality of life while reducing hospitalization rates for COPD exacerbation in patients with moderate-to-severe or severe-to-very severe stable COPD, as compared with the SFC alone or TIO alone group. Although further evaluation is required, the clinical potency of "triple" therapy may prevent further increases in COPD deaths over the next 10 years.

Finally, we should not forget that the synergistic effects of SFC are partly due to the availability of single inhaler devices that contain both medications at relatively low cost, which enhances patient compliance together with improving health status and quality of life.

Disclosure

This manuscript has been read and approved by the author. This paper is unique and is not under consideration by any other publication and has not been published elsewhere. The author and peer reviewers of this paper report no conflicts of interest. The author confirms that they have permission to reproduce any copyrighted material.

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