Comparison and optimal use of fixed combinations in the management of COPD

Mirjam Mensing
René Aalbers

Department of pulmonolgy, Martini Hospital, Groningen, The Netherlands

Abstract: Chronic obstructive pulmonary disease (COPD) is a leading cause of morbidity and mortality worldwide. Indications for the use of long-acting β_2-agonists (LABAs) and inhaled corticosteroids (ICS) in patients with COPD are described in the various international guidelines, but no special recommendations are made concerning the use of combination inhalers containing a LABA as well as an ICS. To determine the place of combination inhalers in the treatment of COPD we reviewed recent literature concerning this subject. On molecular level ICS/LABA combination therapy has anti-inflammatory properties which cannot be attributed to ICS alone. All clinical studies indicate that the two available combinations (salmeterol/fluticasone and formoterol/budesonide) significantly reduce exacerbation rate of moderate/severe exacerbations when compared with placebo. Some studies also showed a significant reduction in exacerbation rate compared with LABA monotherapy, but not compared with ICS monotherapy. From the patient's perspective, ICS/LABA combination inhalers are the first choice when both need to be prescribed, possibly improving patient compliance for ICS. Currently little evidence is available to predict if flexible treatment with LABA/ICS combination inhalers will improve disease control in COPD. Further studies are needed to elucidate the clinical benefit of combination inhalers versus the individual components in different inhalers, and to investigate the clinical benefit of flexible dosing of combination inhalers in patients with COPD.

Keywords: COPD, long-acting β_2-agonists, inhaled corticosteroids.

Introduction

Chronic obstructive pulmonary disease (COPD) is a leading cause of morbidity and mortality worldwide, and results in an economic and social burden that is both substantial and increasing (GOLD 2006). Tobacco smoking is the main risk factor for COPD, although other inhaled noxious particles and gases may contribute to the development of COPD. The treatment of stable COPD consists primarily of smoking cessation, pharmacological intervention with bronchodilators and corticosteroids, long-term oxygen treatment, and pulmonary rehabilitation. Three types of bronchodilator are in common clinical use: β_2-agonists, anticholinergic drugs (both short and long acting), and methylxanthines.

Indications for the use of long-acting β_2-agonists (LABAs) and inhaled corticosteroids (ICS) in patients with COPD are described in the various international guidelines. However, as the definition and classification of COPD differs in four major guidelines, ie, the Global Initiative for Chronic Obstructive Lung Disease (GOLD), British Thoracic Society (BTS), the British National Institute for Clinical Excellence (NICE), and American Thoracic Society (ATS)/European Respiratory Society (ERS) guidelines (BTS 1997; Celli and MacNee 2004; NICE 2004; GOLD 2006), the recommendations for treatment with LABAs and ICS also differ. The GOLD guidelines (GOLD 2006) recommend prescribing a LABA starting at stage II (forced expiratory volume in 1 s

Correspondence: Mirjam Mensing
Afd. Longziekten, Martini Ziekenhuis, Postbus 30033, 9700 RM Groningen, The Netherlands
Tel + 31 50 524 7817
Fax + 31 50 524 5724
Email m.mensing@mzh.nl

[FEV_1] ≥50% but <80%) whereas the ATS/ERS taskforce (Celli and MacNee 2004) recommend starting with a LABA when symptoms persist whilst using as-needed short-acting bronchodilators. Since the BTS guidelines date from 1997 (BTS 1997), they state that at that time only limited evidence for the efficacy of LABAs in COPD was available. At the time the BTS guidelines were formulated, the use of a LABA was only recommended in patients who demonstrated a bronchodilatory response to β_2-agonists, with efficacy being monitored by assessment of symptoms and FEV_1.

The NICE guidelines (NICE 2004), developed with the involvement of members of the BTS, state LABAs should be used in patients who remain symptomatic despite treatment with short-acting bronchodilators and in patients with two or more exacerbations per year.

All guidelines acknowledge that regular treatment with ICS is appropriate for patients with symptomatic COPD and an FEV_1 <50% who experience repeated exacerbations.

In all four guidelines no special recommendations are made concerning the use of combination inhalers containing a LABA as well as an ICS except to suggest their use if both drugs are being prescribed concomitantly.

Since combination inhalers containing ICS and LABAs have become commonly available for the treatment of patients with pulmonary disorders, more data concerning their use in patients with COPD now exists. This paper discusses the possible advantages of using LABA/ICS combination inhalers over using the separate components; the clinical importance of differences between the two available inhalers: salmeterol/fluticasone and budesonide/formoterol; safety and tolerability; and the possibilities of flexible dosing.

Efficacy of combination treatment in COPD

In order to assess the additive effect of combination treatment in patients with COPD, it is imperative to consider the effect of treatment at different levels: molecular level, population level, and individual level.

Molecular level

There is evidence that not only do ICS target the inflammatory process and LABAs cause bronchodilation, but also that there is considerable interaction between the two components. Corticosteroids have been shown to increase β_2-receptor mRNA and reverse receptor downregulation caused by prolonged exposure to β_2-agonists (Brodde et al 1988; Mak et al 1995a, 1995b). In addition, there is persuasive evidence that in asthma, β_2-agonists also target certain aspects of the inflammatory process (Wallin et al 1999; Jeffery et al 2002). In patients with COPD, Haque and colleagues (2006) recently showed that the addition of salmeterol 50 μg to fluticasone 100 μg resulted in an enhancement of glucocorticoid receptor nuclear translocation in macrophages that was equivalent to increasing the fluticasone dose fivefold.

A recent study by Barnes and colleagues (2006) in patients with COPD showed a broad spectrum of anti-inflammatory effects after 13 weeks' treatment with salmeterol and fluticasone that were not seen with placebo. A reduction in lung tissue obtained through endobronchial biopsies CD8+, CD45+, and CD4+ cell counts, sputum differential neutrophils, and total eosinophils and cells expressing genes for tumor necrosis factor-α and interferon-γ was seen in both current and former smokers with COPD (Table 1). A similar study in which fluticasone propionate at the same dose and for the same duration was used alone to treat patients reported no effects on the number of biopsy subepithelial CD8+ or CD4+ cells in lung tissue (Gizycki et al 2002; Hattotuwa et al 2002). In other research (Gosman et al 2006), 6 months' treatment with fluticasone (500 μg twice daily [bid]) in patients with COPD reduced bronchial CD4 cell counts, whereas fluticasone and salmeterol treatment (500/50 μg bid) showed additional reductions in CD8 cells. In a similar study, Yamauchi and colleagues (2006) observed a significant reduction in the number of CD8 and MBP+ cells and a modest reduction in CD68 cells after 3 months' treatment with salmeterol/fluticasone. Treatment with fluticasone alone did cause a reduction in MBP+ cells but failed to do so for CD8 and CD68 cells. These results imply that ICS/LABA combination therapy in COPD has anti-inflammatory properties which cannot be attributed to ICS alone.

Population level

It is still unclear whether the pharmacological interaction observed between LABAs and ICS has an additive effect or a synergistic effect on clinical parameters in COPD. A pharmacological interaction has been suggested in asthma (Zetterstrom et al 2001), but no research has been performed in COPD comparing the effect of a LABA and ICS in separate inhalers versus a combination inhaler. A meta-analysis (Nelson et al 2003) of the effects of co-deposition of fluticasone and salmeterol in patients with asthma showed a significant increase in peak expiratory flow (PEF) compared with separate inhaler treatment. Although some questions were raised about the clinical importance of the size of the improvement (Lipworth and Fardon 2004; Metcalfe and Moodie 2004), the concept of a synergistic

Table 1 Effects of salmeterol/fluticasone and fluticasone propionate on inflammatory cell outcomes (fully published papers only)

Reference	Medication	Duration	Inflammatory cell outcomes
Barnes et al 2006	Salmeterol/fluticasone (SF) 50/500 μg (n = 55)	13 weeks	• SF significantly reduced the absolute numbers of biopsy (CD45+) leukocytes, CD8+ cells, and CD4+ cells.
	versus		• In biopsy SF significantly decreases cells expressing genes for TNF-α and IFN-γ.
	placebo (n = 69)		• No significant CD8:CD4 ratio differences or number of CD68+ cells.
Gizycki et al 2002	Fluticasone Propionate (FP) 500 μg bid (n = 14)	3 month	• Compared with baseline, FP treatment had no significant effects on the total number of inflammatory cells, lymphomononuclear cells, or macrophages in the airway mucosa.
	versus		• Compared with baseline and placebo FP did show a significant reduction in the number of mucosal mast cells.
	placebo (n = 10)		• Compared with placebo the FP group had significantly more neutrophils after treatment.
Hattotuwa et al 2002	Fluticasone propionate (FP) 500 μg bid (n = 16)	3 month	• No significant change in CD3+, CD8+, CD45, CD45Ro+ cells, neutrophils, macrophages, mast cells and eosinophils between baseline and end treatment.
	versus		• No significant reduction in neutrophils compared with placebo treatment. In comparison with placebo mast cells showed a 25% decrease in number in the subepithelium after FP (p = 0.04).
	placebo (n = 14)		• Significant reduction in the numbers of mucosal mast cells.
			• A reduction in the CD8:CD4 ratio in the epithelium and the numbers of subepithelial mast cells in the FP group.
			• CD4+ cells were significantly raised in the placebo group in both epithelium and subepithelium

Abbreviations: FP, fluticasone propionate; PF, ; SF, salmeterol/fluticasone.

effect in a clinical setting remains intriguing. Further research in COPD comparing ICS/LABA combination therapy via a single inhaler versus separate inhalers will help to elucidate this issue further.

In the mean time, many studies (Mahler et al 2002; Calverley et al 2003a, 2003b; Dal Negro et al 2003; Hanania et al 2003; Szafranski et al 2003; Wouters et al 2005) have been performed in COPD using both the salmeterol/fluticasone and budesonide/formoterol combinations to examine the clinical efficacy of a combination inhaler compared with placebo and the individual components. Besides changes in $FEV_{1,}$ most studies included parameters such as symptom scores, quality of life scores, and exacerbation frequency. Exacerbations not only influence quality of life in patients with COPD (Seemungal et al 1998), but also have an independent negative impact on patient prognosis (Soler-Cataluna et al 2005). Acute severe exacerbations in COPD increase mortality, particularly if these exacerbations require hospital admission. Historical cohort studies (Mapel et al 2006a) and retrospective studies (Soriano et al 2003) suggest a positive effect on mortality for combined treatment with LABA and ICS. A recent study by Mapel and colleagues (2006b) showed the use of combination salmeterol/fluticasone or concurrent ICS and LABA was consistently associated with significantly improved survival in patients with COPD compared with those using short acting β_2-agonists alone. With this in mind, the data from the TORCH (TOwards a Revolution in COPD Health) study group (Vestbo 2004) will be of particular interest. The TORCH survival study is a placebo-controlled trial investigating all-cause mortality as the primary endpoint in over 6000 patients randomized to receive salmeterol/fluticasone propionate (50/500 μg bid), salmeterol (50 μg bid), fluticasone propionate (500 μg bid), or placebo for 3 years. Secondary endpoints include COPD exacerbation

rate and health status measured by the St George's Respiratory Questionnaire. Preliminary results show (GSK 2006) a 17% relative reduction in mortality, and a 25% reduction in exacerbations, for patients receiving salmeterol/fluticasone as compared with patients on placebo.

Combination therapy with salmeterol/fluticasone

Mahler and colleagues (2002) and Hanania and colleagues (2003) showed in studies of patients with COPD (Table 2) that 24 weeks' treatment with salmeterol/fluticasone (50/500 μg bid in the Mahler study and 25/500 μg bid for Hanania) significantly increased PEF compared with the individual components and placebo. Interestingly, the Mahler study mentioned that the mean overall change from baseline in morning PEF with salmeterol/fluticasone treatment (31.9 L/min) was greater than the sum of the mean changes from baseline observed with the individual components (12.9 and 16.8 L/min for fluticasone and salmeterol, respectively). However, it is important to note that the actual difference in PEF was very small, and that the value of PEF measurements in COPD is limited. The TRISTAN (TRial of Inhaled STeroids ANd long-acting β_2 agonists) (Calverley et al 2003a) study (Table 2) demonstrated that after 12 months' treatment, the group receiving salmeterol/fluticasone (50/500 μg bid) had both pretreatment and post-treatment FEV_1s that were significantly greater than observed in the other treatment groups (salmeterol monotherapy, fluticasone monotherapy, or placebo), indicating that salmeterol/fluticasone combination inhalers significantly improve FEV_1 and PEF versus the individual components. After post hoc analyses Calverley and colleagues (2006) concluded that, in the subgroup with a baseline FEV_1 <50%, the improvement in lung function for the salmeterol/fluticasone group was twice the sum of the individual components. This suggests a synergistic effect of salmeterol and fluticasone in patients with more severe disease, but only additive effect in patients with mild disease (Singh 2006). Since fluticasone had no significant effect in patients with the most severe disease, it could be argued that salmeterol "unlocks" corticosteroid insensitivity in these patients leading to a true synergistic effect.

Both the Mahler and the Hanania studies showed a significant decrease in rescue medication use in the combination therapy group compared with the placebo and fluticasone groups; the TRISTAN study also demonstrated a significant decrease compared with the salmeterol group.

Neither the pooled data from the Mahler and Hanania studies, which were reported in a Cochrane review (Nannini et al 2004), nor the data from the TRISTAN group showed a significant difference in the odds of experiencing an exacerbation or the exacerbation rate when comparing salmeterol/fluticasone treatment against fluticasone or salmeterol treatment. The post hoc analyses of the TRISTAN data (Calverley et al 2006) showed a higher proportion of patients experienced an exacerbation (60%) in the severe population (FEV_1 <50% predicted) as compared with those in the FEV_1 ≥50% predicted subgroup (44%). With all treatments, reductions in exacerbations rates compared with placebo were statistically significant in subjects with more severe COPD (FEV_1 <50% predicted), but not significant in those with FEV_1 ≥50% predicted.

Although designed differently to the trials mentioned above, the COSMIC (COPD and Seretide: Multi-Center Intervention and Characterization) study revealed similar results (Wouters et al 2005). After a 3-month run-in period with salmeterol/fluticasone, patients were randomized to receive either salmeterol/fluticasone or salmeterol alone. After 1 year's treatment, the salmeterol/fluticasone group experienced a significantly smaller decline in FEV_1 and PEF compared with the salmeterol group, but again no significant difference was found in exacerbation rate.

A significant difference in the mean number of exacerbations per year was found in a pilot study by Dal Negro and colleagues (2003). In this study patients with moderate COPD, who were already treated with theophylline, received additional treatment with salmeterol/fluticasone (50/250 μg bid), salmeterol (50 μg) alone or placebo. The combination treatment resulted not only in greater improvements of respiratory function (such as FEV_1 and morning PEF) and symptom scores compared with salmeterol alone or placebo, but also significantly reduced the mean number of exacerbations per year compared with the year before entering the study. Something that was not seen in the groups receiving salmeterol alone or placebo. However, this reduction from 3.5 to 1.2 exacerbations/year cannot be compared with any of the other studies since all exacerbations, from mild to severe, were taken into account (Table 2). No additional analyses was done for moderate and severe exacerbations alone.

Combination therapy with budesonide/formoterol

Szafranski and colleagues (2003) performed a 12-month study in patients with COPD (Table 3), which demonstrated a

Table 2 Inclusion criteria and definitions of studies using fluticasone propionate and salmeterol

	Treatment	Inclusion criteria	Exacerbation definition
Mahler et al 2002	Salmeterol/fluticasone *versus* fluticasone propionate, salmeterol or placebo	FEV_1/FVC ≤70% FEV_1 <65% predicted normal and >0.70L	Exacerbation was defined by treatment and resulted in withdrawal from the study
Hanania et al 2003	Salmeterol/fluticasone *versus* fluticasone propionate, salmeterol or placebo	FEV_1/FVC ≤70% FEV_1 <65% predicted normal and >0.70L	Moderate exacerbation: requiring treatment with . antibiotics and/ or corticosteroids Severe exacerbation: requiring hospitalization Discontinuation after 1 exacerbation with inhaled or oral corticosteroids or hospitalization or 3 exacerbations treated with antibiotics
TRISTAN Calverley et al 2003a	Salmeterol/fluticasone *versus* fluticasone propionate, salmeterol or placebo	FEV_1/FVC ≤70% FEV_1 25%–70% predicted normal Reversibility after 400 μg salbutamol: <10% of predicted normal. At least one exacerbation per year in the last three years. At least one exacerbation in the year immediately before the trial entry requiring treatment with oral corticosteroids, antibiotics or both.	Exacerbation: a worsening of COPD symptoms that required treatment with antibiotics, oral corticosteroids or both. Episodes that required corticosteroids treatment of hospital admission were noted separately.
Dal Negro et al 2003	Salmeterol/fluticasone *versus* salmeterol or placebo	FEV1/FVC ≤70% FEV1 ≤80% predicted normal and >0,80L Reversibility after 400 μg salbutamol: ≤12% as a percent of predicted normal Regular treatment with 200 mg theophylline bid	Mild exacerbation: condition requiring salbutamol prn >2 occasions/24 h period on 2 or more consecutive days compared with the baseline mean of last 7 days of run-in; Moderate exacerbations: condition requiring treatment with antibiotics and/or oral corticosteroids; Severe exacerbations: condition requiring emergency hospital treatment and/or hospitalization.

Abbreviations: COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity

significantly greater improvement in FEV_1 with budesonide/formoterol (160/4.5 μg bid) versus budesonide (200 μg bid) (9%) and placebo (15%), but not versus formoterol 4.5 μg bid (1%). Budesonide/formoterol significantly prolonged time to first exacerbation compared with all other treatments. However, the rate of severe exacerbations was only significantly lower in the combination treatment group (1.42 exacerbations/patient/year) compared with formoterol (1.84) or placebo (1.87), but not compared to budesonide (1.59). Interestingly, combination treatment did reduce the rate of mild exacerbations (defined as a day with ≥4 inhalations of reliever medication above the mean run-in use) by 35% versus budesonide and by 15% versus formoterol, suggesting a difference either in the mechanisms underlying mild and severe exacerbations or a problem with the definitions of exacerbation types. The differences found between severe and mild exacerbations might also explain the large differences in total exacerbations found in the Dal Negro study.

The Szafranski study also revealed that treatment with the budesonide/formoterol combination was associated with a significantly lower total symptom score compared with placebo and budesonide monotherapy and

Table 3 Inclusion criteria and definitions of studies using budesonide and formoterol

	Treatment	Inclusion criteria	Exacerbation definition
Szafranski et al 2003	Budesonide/formoterol *versus* budesonide, formoterol or placebo	$FEV_1/FVC \leq 70\%$ $FEV_1 \leq 50\%$ predicted normal ≥ 1 severe COPD exacerbation within 2–12 month of first study visit.	Severe exacerbation: use of oral steroids and/or antibiotics and/or hospitalization due to respiratory symptoms.
Calverley et al 2003b	Budesonide/formoterol *versus* budesonide, formoterol or placebo	$FEV_1/FVC \leq 70\%$ $FEV_1 \leq 50\%$ predicted normal ≥ 1 COPD exacerbation requiring antibiotics and/or oral corticosteroids within 2–12 month of first study visit.	Exacerbations were defined by the required medical intervention: oral antibiotics and/or corticosteroids or hospitalization.

Abbreviations: COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity.

significantly reduced reliever medication use (by 1.3 and 0.7 inhalations/24 h, respectively).

Calverley and colleagues (2003b) studied the ability of different inhalation therapies to maintain the improvement in lung function seen after treatment with oral corticosteroids and bronchodilators in patients with COPD. Besides a significant reduction in the exacerbation rate with budesonide/formoterol (320/9 μg bid) compared with placebo and formoterol (9 μg bid), the time to the first exacerbation was significantly prolonged not only with placebo and formoterol but also with budesonide (254, 178, 154, and 96 days for budesonide/formoterol, budesonide, formoterol, and placebo respectively).

Thus, while some of the results suggest that the mean overall change for the combination inhalers is greater than the sum of the mean changes for the individual components (Mahler et al 2002), the results from these trials have not addressed the question of synergistic effects. The TRISTAN data do however suggest a possible synergistic effect would be more pronounced in COPD patients with more severe disease. Further research comparing combination therapy delivered via single versus two separate inhaler devices could elucidate this issue more clearly (Nannini et al 2004).

A conclusive efficacy comparison between the two combination inhalers is difficult based on the studies available, since no head to head study has been performed to date. What can be said is that both combinations led to a significant reduction in exacerbation rate when compared against placebo; but in comparison with ICS monotherapy, both combinations were unable to show a significant reduction in exacerbation rate. When compared with their constituent LABA, a significant reduction in the exacerbation rate was seen for budesonide/formoterol (Szafranski et al 2003) but not for salmeterol/fluticasone (Calverley et al 2003a; Nannini et al 2004). This difference could be the result of a disparities in baseline FEV_1, since the patients in the Szafranski study had a lower mean FEV_1 compared with the TRISTAN study (36%–37% predicted versus 44.2%–45.0% predicted, respectively). Indeed, in the TRISTAN study, the decrease in exacerbation rate was more pronounced in patients with severe disease. Patients with a baseline FEV_1 <50% showed a 30% reduction in exacerbations with the combination treatment compared with placebo whereas patients with a baseline FEV_1 >50% showed only a 10% reduction.

To complicate matters, in a recent article Suissa (2006) criticized, among others, the TRISTAN study for not taking into account the between-subject variation when calculating the exacerbation rate, thus producing artificial statistical significance.

Individual level

In almost all chronic diseases that are being treated pharmacologically, medication adherence and patient compliance form a major problem (Haynes et al 2005). Although no solid data are available about the compliance of patients with COPD in general practice with the use of inhaler medication, compliance rates of 71% reported in clinical trial settings are not very encouraging (van Grunsven et al 2000).

Interviews of patients with asthma showed that many failed to take their preventive medication regularly (Haughney et al 2004). Moreover, the majority of respondents used their reliever medication most frequently because they want to perceive relief from their symptoms immediately. The issue of not taking preventive medication regularly

might be an even larger problem in patients with COPD, since the long-term effects of ICS are less obvious in this disease. For example, ICS are less effective at preventing an exacerbation in COPD (a reduction of 15%–20% versus placebo) than in asthma (a reduction of almost 50% in severe asthma) (Calverley 2004). Patients with asthma were also reported to be very resistant to a treatment regimen that is more complicated than their current two inhaler system ("reliever" and "preventer" medication), ideally preferring a single inhaler treatment (Haughney et al 2004). A retrospective, observational, 24-month database study (Stoloff et al 2004) of medication refills in patients with asthma showed that those receiving salmeterol/fluticasone combination treatment obtained significantly more refills compared with the number of fluticasone refills alone. It was thus concluded that salmeterol/fluticasone in one inhaler might increase ICS refill persistence compared with either fluticasone alone in a single inhaler or fluticasone in combination with salmeterol from two separate inhalers.

The preference for single inhaler treatment combined with the desire for rapid symptom relief is likely to be the same for patients with COPD. This would make combination inhalers containing ICS and LABAs the first choice of treatment when both need to be prescribed to patients with COPD.

Differences between combinations

As mentioned above, the two combination inhalers are difficult to compare since no long-term head to head comparisons have been performed in COPD. In patients with moderate to severe COPD, comparison of the bronchodilator effect of salmeterol/fluticasone (50/250 μg) and budesonide/formoterol (12/400 μg) showed that both inhaled combinations are effective at improving airflow limitation after acute administration (Cazzola et al 2003). This study did show a trend for a faster onset of action for budesonide/formoterol, but the differences between the two inhalers were only significant after 120 min. The clinical meaning of this faster onset of action, however, is questionable for patients with COPD who are in need of sustained bronchodilation.

When it comes to inhalation treatment delivery systems, metered-dose inhalers (MDIs) and jet nebulizers are equally effective in elderly patients, although most patients consider the MDI to be more acceptable and the jet nebulizer to be more effective (Balzano et al 2000). Comparing the Diskus® (Advair, GlaxoSmithKline, Pittsburgh, PA) with the Turbuhaler® (AstraZeneca, Wilmington, DE) dry-powder inhalers (DPIs), patients make significantly fewer errors in essential inhalation maneuvers when using a Diskus/Accuhaler. However, the clinical relevance of these findings is uncertain, since no lung function tests were performed to assess the effectiveness of the inhaled medication (van der Palen et al 1998).

Research performed by the manufacturer of the Diskus (GlaxoSmithKline) showed that in patients with COPD and a $FEV_1 \leq 30\%$ predicted, the inspiratory flow was significantly higher through the Diskus than the Turbuhaler (Burnell et al 2001). Moreover, the Diskus was shown to deliver a more consistent dose irrespective of flow than the Turbuhaler in this population. However, again, no assessment of effectiveness was made in this context.

Given the few head to head comparisons of the two combination treatments, no real advantage can be deducted for either inhaler from a patient's perspective.

Safety and tolerability of combination treatment in COPD

Given the large proportion of patients with COPD who have co-morbidities, safety is a cardinal issue in COPD treatment.

The Mahler study (Mahler et al 2002) found no significant differences with respect to cardiac problems when comparing Holter monitor results between the treatment groups. Neither the Szafranski study (Szafranski et al 2003), the Mahler study (Mahler et al 2002), nor the TRISTAN study group (Calverley et al 2003a) found any clinically significant changes in electrocardiograms that could be attributed to treatment.

Pooled analysis in a Cochrane review (Nannini et al 2004) of the Mahler, TRISTAN, and Hanania studies showed that oropharyngeal candidiasis occurred more frequently in the fluticasone/salmeterol treatment group than in the groups given placebo or salmeterol monotherapy. However, there was no significant difference in the odds of oropharyngeal candidiasis affecting those treated with fluticasone/salmeterol compared with fluticasone.

The TRISTAN study did show a significant difference in serum cortisol concentrations between fluticasone and placebo at Week 24 and Week 52, and between fluticasone/salmeterol and placebo at Week 24. None of the changes were associated with any clinical effects or signs of hypoadrenalism. The Mahler study (Mahler et al 2002) reported no differences in prestimulated morning plasma cortisol concentrations between the treatment groups or differences in inappropriate cortisol response to stimulation.

Overall, the combination treatments would thus appear to be as well tolerated as treatment with the individual components.

Flexible dosing

Currently, combination inhalers are prescribed as maintenance treatment in COPD using fixed dosing (Celli and MacNee 2004; GOLD 2006). In asthma, however, research has examined the possibilities of using combination inhalers more flexibly. Since no such studies have yet been performed in COPD, it is hard to predict the possibilities of such approaches in this indication. Although it is tempting to assume that study results would show a similar clinical benefit in COPD as they do in asthma, one has to keep in mind that the diseases differ from each other in many respects.

Two different regimens of flexible dosing with ICS/LABA have been studied in asthma: combination therapy as both maintenance and reliever medication (O'Byrne et al 2005) and adjustable maintenance dosing (AMD) (Aalbers et al 2004). Using a combination inhaler for maintenance as well as reliever medication might be a possibility in patients with COPD who are used to taking short-acting bronchodilators when needed. Research examining the effects of using formoterol as maintenance treatment and reliever medication (Campbell et al 2005) showed that this concept does work in patients with COPD, resulting in a significant improvement in FEV_1 compared with formoterol bid and terbutaline as needed. Unfortunately no improvements were seen in other parameters, such as symptom scores, reliever use, or health-related quality of life, which are so important for patients with COPD. It has to be said that this flexible approach has only been investigated in asthma for the budesonide/formoterol combination, since this combination gives significantly faster bronchodilation than salmeterol/fluticasone in acute severe asthma (van der Woude et al 2004). As mentioned above, this difference seems to be less pronounced in patients with COPD (Cazzola et al 2003).

The alternative AMD approach allows patients to increase their maintenance dosing during a limited period of time whenever they experience an increase in symptoms. Although changes in PEF and FEV_1 are usually small to begin with, exacerbations in COPD are accompanied by a clear deterioration of symptoms (Seemungal et al 2000; Wedzicha and Donaldson 2003). Hence, adjustment of maintenance dosing based on symptoms and, perhaps, reliever medication use might be possible in patients with COPD who have a clear perception of their disease. Studies using patient diary cards (Seemungal et al 1998) show that about half of exacerbations (defined as worsening of the COPD symptoms) are not reported by the patient to their investigator, even when they are urged to do so. This suggests that by leaving the patient in charge of adjusting their maintenance medication based on symptoms, at least some treatment of unreported worsenings of the disease will take place. If an intervention such as the AMD approach will lead to a decrease in the level of severe exacerbation remains to be seen. This approach is partly based on self-management of the disease, a concept that has been proven successful in asthma (Toelle and Ram 2004) but is still under debate in COPD (Monninkhof et al 2003). Nevertheless, recent studies show that self-management in COPD can lead to a reduction of hospital admissions due to an exacerbation (Bourbeau et al 2003) and may decrease the number of exacerbations experienced (Hutchinson et al 2006).

There is currently little evidence to predict if flexible treatment with LABA/ICS combination inhalers will improve disease control in COPD. However, based on results in patients with asthma, this treatment option seems worth investigating in COPD.

Conclusion

There is some evidence to suggest that using a combination inhaler is preferable to using the individual components separately in COPD when both components are prescribed. A vast number of studies demonstrated an improvement in symptom scores, PEF, FEV_1, reliever medication use, and, possibly, exacerbation rates when the use of combination inhalers is compared with that of the individual components in COPD. However, it remains unclear if there is anything to be gained from using combination inhalers in patients with less severe COPD. The clinical studies presented here mostly used FEV_1 <65% or FEV_1 ≤50% of predicted normal as an inclusion criterion. The TRISTAN study was the only large study to also include COPD patients with less severe COPD. They demonstrated a greater reduction in the exacerbation rate for the group with an FEV_1 <50% predicted compared with the patients with an FEV_1 >50% predicted. It will be interesting to see if other studies, including more mild cases of COPD, will come to the same conclusion.

As for the differences between the two available combinations (budesonide/formoterol and salmeterol/fluticasone), there is no evidence to suggest an advantage for one product over the other. The usage of the inhalers themselves is somewhat different, possibly leading to different mistakes being made by patients while using them. It is therefore important for the treating physician to be attentive towards any mistakes in patients' inhalation technique. If patients frequently make the same errors, the physician should consider changing the patient's device.

The option to recommend the use of a combination inhaler in a self-management plan in patients with COPD is a possibility well worth exploring in the future.

References

Aalbers R, Backer V, Kava TT, et al. 2004. Adjustable maintenance dosing with budesonide/formoterol compared with fixed-dose salmeterol/fluticasone in moderate to severe asthma. *Curr Med Res Opin*, 20:225–40.

Balzano G, Battiloro R, Biraghi M, et al. 2000. Effectiveness and acceptability of a domiciliary multidrug inhalation treatment in elderly patients with chronic airflow obstruction: metered dose inhaler versus jet nebulizer. *J Aerosol Med*, 13:25–33.

Barnes NC, Qiu YS, Pavord ID, et al. 2006. Antiinflammatory effects of salmeterol/fluticasone propionate in chronic obstructive lung disease. *Am J Respir Crit Care Med*, 173:736–43.

Bourbeau J, Julien M, Maltais F, et al. 2003. Reduction of hospital utilization in patients with chronic obstructive pulmonary disease: a disease-specific self-management intervention. *Arch Intern Med*, 163:585–91.

Brodde OE, Howe U, Egerszegi S, et al. 1988. Effect of prednisolone and ketotifen on beta 2-adrenoceptors in asthmatic patients receiving beta 2-bronchodilators. *Eur J Clin Pharmacol*, 34:145–50.

[BTS] British Thoracic Society. 1997. BTS guidelines for the management of chronic obstructive pulmonary disease. The COPD Guidelines Group of the Standards of Care Committee of the BTS. *Thorax*, 52:S1–28.

Burnell PK, Small T, Doig S, et al. 2001. Ex-vivo product performance of Diskus and Turbuhaler inhalers using inhalation profiles from patients with severe chronic obstructive pulmonary disease. *Respir Med*, 95:324–30.

Calverley P, Pauwels R, Jones P, et al. 2006. The severity of airway obstruction as a determinant of treatment response in COPD. *Int J COPD*, 1:209–18.

Calverley P, Pauwels R, Vestbo J, et al. 2003a. Combined salmeterol and fluticasone in the treatment of chronic obstructive pulmonary disease: a randomised controlled trial. *Lancet*, 361:449–56.

Calverley PM. 2004. Effect of corticosteroids on exacerbations of asthma and chronic obstructive pulmonary disease. *Proc Am Thorac Soc*, 1:161–6.

Calverley PM, Boonsawat W, Cseke Z, et al. 2003b. Maintenance therapy with budesonide and formoterol in chronic obstructive pulmonary disease. *Eur Respir J*, 22: 912–19.

Campbell M, Eliraz A, Johansson G, et al. 2005. Formoterol for maintenance and as-needed treatment of chronic obstructive pulmonary disease. *Respir Med*, 99:1511–20.

Cazzola M, Santus P, Di Marco MF, et al. 2003. Bronchodilator effect of an inhaled combination therapy with salmeterol + fluticasone and formoterol + budesonide in patients with COPD. *Respir Med*, 97:453–7.

Celli BR, MacNee W. 2004. Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. *Eur Respir J*, 23:932–46.

Dal Negro RW, Pomari C, Tognella S, et al. 2003. Salmeterol & fluticasone 50 microg/250 microg bid in combination provides a better long-term control than salmeterol 50 microg bid alone and placebo in COPD patients already treated with theophylline. *Pulm Pharmacol Ther*, 16:241–6.

Gizycki MJ, Hattotuwa KL, Barnes N, et al. 2002. Effects of fluticasone propionate on inflammatory cells in COPD: an ultrastructural examination of endobronchial biopsy tissue. *Thorax*, 57:799–803.

[GSK] GlaxoSmithKline. 2006. Press release [online]. Accessed 30 June 2006. URL: http://www.gsk.com.

[GOLD] Global Inititive for Chronic Obstructive Lung Disease. 2006. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: executive summary (updated 2006) [online]. Accessed 1 June 2007. URL: http://www.goldcopd.org.

Gosman MME, Lapperre TS, Snoeck-Stroband JB, et al. 2006. Effect of 6 month therapy with inhaled fluticasone propionate (FP) with or without salmeterol (S) on bronchial inflammation in COPD [abstract]. *ATS conference*, A111.

Hanania NA, Darken P, Horstman D, et al. 2003. The efficacy and safety of fluticasone propionate (250 microg)/salmeterol (50 microg) combined in the Diskus inhaler for the treatment of COPD. *Chest*, 124:834–843.

Haque RA, Torrego A, Essilfie-Quaye S, et al. 2006. Effects of salmeterol and fluticasone on glucocorticoid receptor translocation in sputum macrophages and peripheral blood mononuclear cells from patients with chronic obstructive pulmonary disease [abstract]. *ATS conference*, A848.

Hattotuwa KL, Gizycki MJ, Ansari TW, et al. 2002. The effects of inhaled fluticasone on airway inflammation in chronic obstructive pulmonary disease: a double-blind, placebo-controlled biopsy study. *Am J Respir Crit Care Med*, 165:1592–6.

Haughney J, Barnes G, Partridge M, et al. 2004. The Living & Breathing Study: a study of patients' views of asthma and its treatment. *Prim Care Respir J*, 13:28–35.

Haynes RB, Yao X, Degani A, et al. 2005. Interventions to enhance medication adherence. *Cochrane Database Syst Rev*, 4:CD000011.

Hutchinson AF, Thompson MA, Brand CA, et al. 2006. Patient self-management training and a nurse-led rapid assessment service in the community decreases severity of exacerbations and readmission rates in the Melbourne Longitudinal COPD Cohort (MLCC) [abstract]. *ATS conference*, A811.

Jeffery PK, Venge P, Gizycki MJ, et al. 2002. Effects of salmeterol on mucosal inflammation in asthma: a placebo-controlled study. *Eur Respir J*, 20:1378–85.

Lipworth BJ, Fardon TC. 2004. Enhanced synergy between fluticasone propionate and salmeterol inhaled from a single inhaler versus separate inhalers. *J Allergy Clin Immunol*, 113:178–9.

Mahler DA, Wire P, Horstman D, et al. 2002. Effectiveness of fluticasone propionate and salmeterol combination delivered via the Diskus device in the treatment of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*, 166:1084–91.

Mak JC, Nishikawa M, Barnes PJ. 1995b. Glucocorticosteroids increase beta 2-adrenergic receptor transcription in human lung. *Am J Physiol*, 268:L41–6.

Mak JC, Nishikawa M, Shirasaki H, et al. 1995a. Protective effects of a glucocorticoid on downregulation of pulmonary beta 2-adrenergic receptors in vivo. *J Clin Invest*, 96:99–106.

Mapel DW, Hurley JS, Roblin D, et al. 2006a. Survival of COPD patients using inhaled corticosteroids and long-acting beta agonists. *Respir Med*, 100:595–609.

Mapel DW, Nelson LS, Lydick E, et al. 2006b. Survival of COPD patients using the Advair (R) diskus, inhaled corticosteroids and salmeterol individually, inhaled corticosteroids alone, or short acting bronchodilators alone [abstract]. *ATS conference*, A110.

Metcalfe S, Moodie P. 2004. Seretide meta-analysis missed important features and overstates any advantages over concurrent LABA/ICS devices. *J Allergy Clin Immunol*, 113:568–9.

Monninkhof E, van der Valk PJ, van der Palen J et al. 2003. Self-management education for patients with chronic obstructive pulmonary disease: a systematic review. *Thorax*, 58:394–8.

Nannini L, Cates CJ, Lasserson TJ, et al. 2004. Combined corticosteroid and long acting beta-agonist in one inhaler for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*, 3:CD003794.

Nelson HS, Chapman KR, Pyke SD, et al. 2003. Enhanced synergy between fluticasone propionate and salmeterol inhaled from a single inhaler versus separate inhalers. *J Allergy Clin Immunol*, 112:29–36.

[NICE] National Institute for Clinical Excellence. 2004. Chronic obstructive pulmonary disease: national clinical guideline for management of chronic obstructive pulmonary disease in adults in primary and secudary care. *Thorax*, 59(Suppl I).

O'Byrne PM, Bisgaard H, Godard PP, et al. 2005. Budesonide/formoterol combination therapy as both maintenance and reliever medication in asthma. *Am J Respir Crit Care Med*, 171:129–36.

Seemungal TA, Donaldson GC, Bhowmik A, et al. 2000. Time course and recovery of exacerbations in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*, 161:1608–13.

Seemungal TA, Donaldson GC, Paul EA, et al. 1998. Effect of exacerbation on quality of life in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*, 157:1418–22.

Singh D. 2006. The benefits of combined treatment with corticosteroids and long-acting beta agonists. *Int J COPD*, 1:207–8.

Soler-Cataluna JJ, Martinez-Garcia MA, Roman SP, et al. 2005. Severe acute exacerbations and mortality in patients with chronic obstructive pulmonary disease. *Thorax*, 60:925–31.

Soriano JB, Kiri VA, Pride NB, et al. 2003. Inhaled corticosteroids with/without long-acting beta-agonists reduce the risk of rehospitalization and death in COPD patients. *Am J Respir Med*, 2:67–74.

Stoloff SW, Stempel DA, Meyer J, et al. 2004. Improved refill persistence with fluticasone propionate and salmeterol in a single inhaler compared with other controller therapies. *J Allergy Clin Immunol.* 113:245–51.

Suissa S. 2006. Statistical treatment of exacerbations in therapeutic trials of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*, 173:842–6.

Szafranski W, Cukier A, Ramirez A, et al. 2003. Efficacy and safety of budesonide/formoterol in the management of chronic obstructive pulmonary disease. *Eur Respir J*, 21:74–81.

Toelle BG, Ram FS. 2004. Written individualised management plans for asthma in children and adults. *Cochrane Database Syst Rev*, 2: CD002171.

van der Palen J, Klein JJ, Schildkamp AM. 1998. Comparison of a new multidose powder inhaler (Diskus/Accuhaler) and the Turbuhaler regarding preference and ease of use. *J Asthma*, 35:147–52.

van der Woude HJ, Boorsma M, Bergqvist PB, et al. 2004. Budesonide/formoterol in a single inhaler rapidly relieves methacholine-induced moderate-to-severe bronchoconstriction. *Pulm Pharmacol Ther*, 17:89–95.

van Grunsven PM, van Schayck CP, van Deuveren M, et al. 2000. Compliance during long-term treatment with fluticasone propionate in subjects with early signs of asthma or chronic obstructive pulmonary disease (COPD): results of the Detection, Intervention, and Monitoring Program of COPD and Asthma (DIMCA) Study. *J Asthma*, 37:225–34.

Vestbo J. 2004. The TORCH (towards a revolution in COPD health) survival study protocol. *Eur Respir J*, 24:206–10.

Wallin A, Sandstrom T, Soderberg M, et al. 1999. The effects of regular inhaled formoterol, budesonide, and placebo on mucosal inflammation and clinical indices in mild asthma. *Am J Respir Crit Care Med*, 159:79–86.

Wedzicha JA, Donaldson GC. 2003. Exacerbations of chronic obstructive pulmonary disease. *Respir Care*, 48:1204–13.

Wouters EF, Postma DS, Fokkens B, et al. 2005. Withdrawal of fluticasone propionate from combined salmeterol/fluticasone treatment in patients with COPD causes immediate and sustained disease deterioration: a randomised controlled trial. *Thorax*, 60:480–7.

Yamauchi Y, Christodoulopoulos P, Maltais F, et al. 2006. The effect of salmeterol/fluticasone combination on airway inflammation in COPD compared to fluticasone [abstract]. *ATS conference*, A113.

Zetterstrom O, Buhl R, Mellem H, et al. 2001. Improved asthma control with budesonide/formoterol in a single inhaler, compared with budesonide alone. *Eur Respir J*, 18:262–8.