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The use of long acting β_2-agonists, alone or in combination with inhaled corticosteroids, in Chronic Obstructive Pulmonary Disease (COPD) A risk–benefit analysis

Alison C. Cave *, Martin M. Hurst

Medicines and Healthcare Products Regulatory Agency, 151 Buckingham Palace Road, London SW1W 9SZ, United Kingdom

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ABSTRACT

Chronic Obstructive Pulmonary Disease (COPD) is a slowly progressive, largely non-reversible pulmonary disease which is characterised by airflow limitation. It is one of the few diseases with an increasing mortality rate and by 2020 it is predicted to be the third leading cause of death. The mainstays of current treatment are long acting β_2 agonists (LABAs) coupled with an increasing reliance on inhaled corticosteroids (ICS). Two LABAs (salmeterol and formoterol) are currently licenced for COPD both as monotherapy and in combination with ICS (fluticasone propionate (FP) and budesonide respectively). A comprehensive review of the risk–benefit of these medicines in COPD is provided here which concludes that there is limited efficacy for LABAs in COPD either alone or in combination with ICS and no overall modification of the disease process. However, where directly compared, combination therapy usually provides an advantage over monotherapy. Importantly the apparent effectiveness of treatment may significantly depend upon the outcome measure chosen with some measures possibly underestimating the extent of benefit. ICS benefit may also be greater in those patients who respond to treatment. Set against this benefit are recent concerns that a number of issues related to the clinical trial design such as prior use of ICS and different withdrawal rates between groups may be significantly influencing results. Furthermore there is no evidence of a dose response relationship with regard to ICS dose. A key issue with combination therapy is the excess risk of pneumonia conferred by the use of an ICS in this patient population. This risk does not appear to be proportional to the ICS dose but may differ between FP and budesonide. We conclude that further studies are required to identify the optimal dose of ICS, in terms of both risk and benefit, and to confirm their benefit in steroid naïve patients. Furthermore it will be important to determine whether the risk of pneumonia is apparent with both FP and budesonide and to identify factors which may predict steroid responsiveness in COPD.

Contents

Abbreviations: ADRs, adverse drug reactions; ATS, American Thoracic Society; BDF, budesonide/formoterol combination; BID, twice a day; BTS, British Thoracic Society; CAP, community acquired pneumonia; CHMP, Committee for Medicinal Products for Human Use; CRP, C-reactive protein; COPD, Chronic Obstructive Pulmonary Disease; CRE, cAMP response element; EBGM, Empirical Bayes Geometric Mean; EMA, European Medicines Agency; ERS, European Respiratory Society; FEV1, forced expiratory volume in 1 second; FP, fluticasone propionate; GOLD, Global Initiative for Chronic Obstructive Lung Disease; GR, glucocorticoid receptor; GRE, glucocorticoid response element; GSK, GlaxoSmithKline Limited; HDAC, histone deacetylase; ICS, inhaled corticosteroids; IL-6, interleukin-6; IMS, Intercontinental Medical Statistics; LABAs, long acting β_2-agonists; LAMA, long acting muscarinic antagonist; LOQ, list of questions; MHRA, Medicines and Healthcare products Regulatory Agency; NICE, National Institute for Health and Clinical Excellence; PKA, protein kinase A; PSUR, periodic safety update report; QID, four times a day; SABA, short acting β_2-agonists; SFC, salmeterol/fluticasone propionate combination (Seretide); SGRQ, St George's Respiratory Score; SOC, System Organ Class; TID, three times a day; TIO, tiotropium bromide; TSM, tracheal smooth muscle; TORCH, Towards a Revolution in COPD Health.

* Corresponding author at: Therapeutic Review Group, MHRA, 151 Buckingham Palace Road, London SW1W 9SZ, United Kingdom. Tel.: +44 20 3080 6107.
E-mail address: Alison.Cave@mhra.gsi.gov.uk (A.C. Cave).

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1. Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a slowly progressive, largely non-reversible pulmonary disease which is characterised by airflow limitation. The disease encompasses multiple structural and functional components but inflammation is at the core of the disease affecting both the lungs and other organs. The main mechanisms that contribute to airflow limitation in COPD are fixed narrowing of small airways, emphysema and luminal obstruction with mucus secretions. COPD affects mainly middle-aged and elderly people (Briggs, 2004) and is caused, in ~90% of cases, by chronic cigarette smoking, although other environmental insults such as the burning of biomass fuels are also major risk factors (Barnes et al., 2003; Rabe, 2007).

The inflammation associated with COPD is thought to be a neutrophilic inflammatory disorder of the small airways and lungs that is maintained at least in part by macrophages and lymphocytes. Local inflammation is known to play a major role in effecting airway remodelling and parenchymal destruction in COPD and contributes to the airflow limitation. Destruction of the lung parenchyma leads to the loss of alveolar attachments in the small airways and decreases lung elastic recoil, limiting the ability of the airways to remain open during expiration. In addition however many COPD patients demonstrate systemic inflammation that is positively associated with disease severity (Sin & Man, 2003). As such biomarkers of inflammation (circulating C-reactive protein (CRP), fibrinogen, tumour necrosis factor α (TNF-α) and blood leukocytes) were all elevated in patients with moderate to severe disease even under stable conditions (Gan et al., 2004). Increased systemic inflammation is a major risk factor for cardiovascular disease and this may be correlated with the fact that over half of COPD patients die from cardiovascular causes (Camilli et al., 1991; Sin & Man, 2003).

Although COPD progression is often thought of as inevitable and continuous, the clinical course is actually quite variable and probably influenced by the frequency of exacerbations. Exacerbations are common especially in severe disease, frequently lead to hospitalisation and can be life threatening. As such, preventing exacerbations with pharmacologic and non-pharmacologic care can influence overall morbidity although smoking cessation is the only intervention currently shown to slow disease progression. Co-morbidities such as lung cancer, cardiovascular disease, and skeletal muscle dysfunction also contribute to declining patient health. Bronchodilators, despite controlling symptoms, have not thus far been demonstrated to reduce the accelerated annual rate of decline in lung function that is characteristic of COPD, suggesting that they do not alter the underlying pathology of the disease.

COPD is currently the fourth leading cause of death in the US and one of the few major diseases associated with a rising mortality rate. By 2020 the Global Burden of Disease Study predicts that COPD will be the third leading cause of death, driven by the expanding epidemic of cigarette smoking and changing demographics e.g. longer life span (Giembycz et al., 2008). The prevalence of COPD in the general population is estimated to be about 1% across all ages rising with age to >10% amongst those aged ≥40 years (Chapman et al., 2006). Since the mid-1990s emergency admissions for COPD have risen by 50% to a total of 98,000 in 2000 whilst admissions for asthma fell over the same period. In the UK, COPD accounts for at least 10% of all medical emergency admissions and 0.9% of all admissions.

Given this rapidly expanding patient population and the recent concerns with regard to the use of long acting β_2 agonists (LABAs) in asthma, the Medicines and Healthcare products Regulatory Agency (MHRA) felt it was an appropriate time to review the risk–benefit of these agents, both when used alone or in conjunction with inhaled corticosteroids (ICS), in COPD. Thus the following review represents a comprehensive analysis of recent studies and spontaneous adverse event reporting of the two LABAs currently licenced for the use in COPD in the UK.

2. Current guidelines

COPD guidelines are issued by the Global Initiative on Obstructive Lung Disease (GOLD) (GOLD guidelines, 2009) and the National Institute of Health and Clinical Excellence (NICE) (National Clinical Guideline Centre, 2010). Both these bodies recommend the addition of LABAs or long acting muscarinic agonists (LAMA) to short acting bronchodilation when moderate COPD is diagnosed and the addition of inhaled corticosteroids or another long acting bronchodilator when the disease progresses to severe (patients with an FEV_1<50% predicted, who are having two or more exacerbations requiring treatment with antibiotics or oral corticosteroids in a 12 month period).

The most recent NICE guideline (Reilly et al., 2010) updated in June 2010 states that a LAMA should be offered in addition to LABAs + ICS in patients which remain breathless or have exacerbations irrespective of their FEV_1. Adding a new medication rather than increasing the dose of an existing therapy may reduce the risk of adverse effects.

3. Current therapy

There are two LABAs currently licenced for COPD in the EU:

Salmeterol both as monotherapy (Serevent; up to 100 μg/day) and in combination with fluticasone propionate (FP) (Seretide; 100 μg/day of salmeterol + 1000 μg/day FP).

Formoterol both as monotherapy (maximum regular daily dose of 24 μg with some products being additionally licenced for symptomatic relief up to a maximum total daily dose of 48 μg) and in combination with budesonide (Symbicort; recommended dose of 24 μg/day formoterol + 800 μg/day budesonide).

4. The clinical pharmacology of formoterol and salmeterol in the management of COPD

Although both formoterol and salmeterol are LABAs with duration of action greater than 12 h they have a very different pharmacology. Both agonists are lipophilic which contributes to their long duration of action and both are highly selective for the β_2 receptor. The primary difference between the two substances lies in:

(i) The rate of onset of action, formoterol being much faster which allows it to be licenced for on demand symptom relief. Around 70% of maximum bronchodilatation is seen within 5 min of inhalation of formoterol compared with nearly an hour for salmeterol. Thus