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PRODUCT REVIEW

Budesonide/Eformoterol (Symbicort®) in the Treatment of COPD:
Focus on Real-World Evidence

Making Education Easy 2018

About the reviewer

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This article reviews the use of budesonide/eformoterol (Symbicort®) in the treatment of patients with chronic obstructive pulmonary disease (COPD) with regard to exacerbations, morning symptoms, pneumonia risk, and treatment response, and with an emphasis on real-world evidence. This review is sponsored by AstraZeneca.

Treatment of COPD

The evidence-based GOLD guidelines affirm that pharmacological therapy for COPD, which includes inhaled bronchodilators and corticosteroids, ameliorates symptoms and reduces the frequency and severity of exacerbations.[1] More specifically, a long-acting beta$_2$-agonist (LABA) bronchodilator combined with an inhaled corticosteroid (ICS) is more effective than either component alone in improving lung function and reducing exacerbations in patients with moderate to severe COPD and a history of exacerbations.[1]

Budesonide/eformoterol (200/6µg or 400/12µg per inhalation) is a fixed-dose ICS/LABA combination delivered via a multidose, inspiratory flow driven, dry powder inhaler (Turbuhaler®) that is indicated in the regular treatment of adult patients with moderate to severe COPD (FEV$_1$ ≤50% of predicted normal) who have frequent symptoms despite beta$_2$-agonist use and a history of exacerbations.* Budesonide/eformoterol is fully subsidised by PHARMAC.

* Symbicort Turbuhater Data Sheet (12 April 2018). AstraZeneca Limited. Available at: www.medsafe.govt.nz.

Real-world evidence

The primary purpose of randomised controlled trials (RCTs) is to establish the *efficacy* of an medical intervention, in the context of a cause-and-effect relationship, for a pre-defined outcome.[2] Because RCTs are considered to be the highest level of medical evidence, most COPD guidelines are based on data generated by RCTs and systematic reviews of RCTs.[2,3]

However, to minimise the influence of confounding factors on the primary clinical outcome, RCTs use highly selected patients with minimal comorbidities and monitoring to ensure treatment adherence.[2] Consequently, it may not be possible to extrapolate data from RCTs to clinical practice populations that are generally unselected, have more comorbidities, and are less adherent to treatment.[2]

Indeed, there is evidence that COPD patients enrolled in typical RCTs are not highly representative of the patient population being treated by respiratory specialists and GPs in everyday clinical practice. A Scandinavian study was conducted to estimate the proportion of an obstructive lung disease (OLD) outpatient population (patients prospectively recruited from three respiratory specialist clinics and nine GPs) that could have been included in an RCT.[3] The application of typical RCT selection criteria selected just 17.2% of the OLD population diagnosed as COPD patients (i.e., eligible patients), representing only 7.2% of the entire OLD population. The RCT selection criterion 'absence of co-morbidity' excluded nearly two-thirds of eligible COPD patients (63.9%).[3] Similarly, a respiratory health survey of NZ adults randomly selected from the community found that only a median of 5% of those with COPD met the inclusion criteria for the major RCTs and >90% of those taking medication were doing so based on the conclusions of RCTs for which they would not have been eligible.[4]

In contrast to RCTs, real-world studies assess the overall *effectiveness* of a medical intervention in large unselected populations, which include patients with comorbidities, and with no formal supervision to ensure adherence.[2] Consequently, the results of real-world studies are probably more applicable to a broader patient population under routine clinical care than RCTs. Electronic health record (EHR) databases are an important source of longitudinal real-world data.[2,5] The authors of a recently published systematic review of UK healthcare guidelines (published between 2007 and 2015), which utilised data from a large general practice database, concluded that real-world evidence has been increasingly used over the last decade to inform clinical practice.[5]

Real-world evidence includes pragmatic RCTs (pRCTs), which are large prospective comparative clinical studies in which patients are randomised to treatment and then followed-up according to usual clinical practice.[2,6] An example of a pRCT is the Salford Lung study, which is a multicentre, controlled effectiveness trial that demonstrated that treatment with fluticasone furoate/vilanterol was associated with a lower rate of exacerbations compared with usual care in a large real-world population of patients with COPD.[7]

Expert comment: As practicing clinicians, part of our job is to interpret the available evidence and recommend the best treatment strategy as applicable to individual patients. There has been a paradigm shift in what is considered best evidence in the last 10–15 years with a re-focus on less selected and tightly controlled studies that may better reflect the real-world patient. The newly-recognised phenotype of asthma-COPD overlap for example, makes up a large proportion of patients with chronic obstructive lung disease. However, there is little high-level evidence informing treatment decisions in this group, as these patients are traditionally excluded from both COPD and asthma RCTs. Pragmatic RCTs and real-world studies help to fill gaps such as these.

Real-world observational studies (often from existing clinical patient databases) usually also consist of larger numbers of patients than is feasible (or cost effective) to include in RCTs. This is advantageous from the point of view of documenting adverse events in real patients often with multiple co-morbidities. For example, the ongoing concern of cardiovascular adverse events associated with bronchodilators in patients with COPD has not been conclusively settled despite multiple RCTs as these tend to exclude patients with high cardiovascular risk profiles.

Real-world studies offer many advantages, but their results still need to be interpreted with caution. The lack of patient selection, a strength for many real-world studies, makes it also impossible to avoid unmeasured confounding factors. There is also confounding by indication where patients are not randomised to treatment, but treatment is selected based on indication. Bias due to lack of blinding is another consideration. These limitations can be mitigated with careful trial design and data analyses with the use of propensity scores for example. On the whole, the evidence from both traditional RCTs and carefully conducted real-world studies complement each other and provide the clinician with different insights into therapeutic options.

Exacerbation reduction

The real-world effectiveness of budesonide/eformoterol has been evaluated in three large cohort studies that assessed exacerbation rates in primary care patients with COPD treated with budesonide/eformoterol compared with fluticasone propionate/salmeterol. (**Table 1**).[8-10] The three studies used propensity score matching to alleviate potential biases resulting from the non-random assignment of patients to treatment. Key findings were that budesonide/eformoterol was associated with statistically significantly greater reductions in exacerbations leading to hospitalisation (in all 3 studies) and exacerbations leading to an emergency department (ED) visit (in the 2 studies that measured this outcome) than fluticasone propionate/salmeterol (**Table 1**).

	Blais et al.[8]	Larsson et al.[9]	Perrone et al.[10]
Design	One-year, population-based, retrospective matched cohort study conducted using administrative health care databases	Population-based, retrospective, observational cohort study (PATHOS) linking data from primary care medical records and from mandatory national registers	Observational retrospective cohort analysis, based on administrative databases of three local health units
Country	Canada	Sweden	Italy
No. of patients	2262	5468	4680
Inclusion criteria	Patients aged >40 years with ≥1 diagnosis for COPD in the year before treatment initiation with a fixed combination of B/F or F/S	Patients with physician-diagnosed COPD and a record of post-diagnosis treatment with a fixed combination of B/F or F/S with ≤11 years follow-up	Patients aged ≥40 years with ≥1 prescription of a fixed combination of B/F or F/S, at dosages and formulations approved for COPD and with ≥6 months follow-up
Propensity score matching	Yes	Yes	Yes
Exacerbations requiring an ED visit*	↓25% (p<0.05)	↓21% (p=0.0003)	Not measured
Exacerbations requiring hospitalisation*	↓39% (p<0.05)	↓29% (p<0.0001)	↓16% (p<0.01)

Table 1. Summary of the design and key findings of three large real-world studies that evaluated the effectiveness of budesonide/eformoterol (B/F) compared with fluticasone propionate/salmeterol (F/S) in patients with COPD. *B/F relative risk reduction versus F/S. Abbreviation: ED = emergency department

Triple therapy

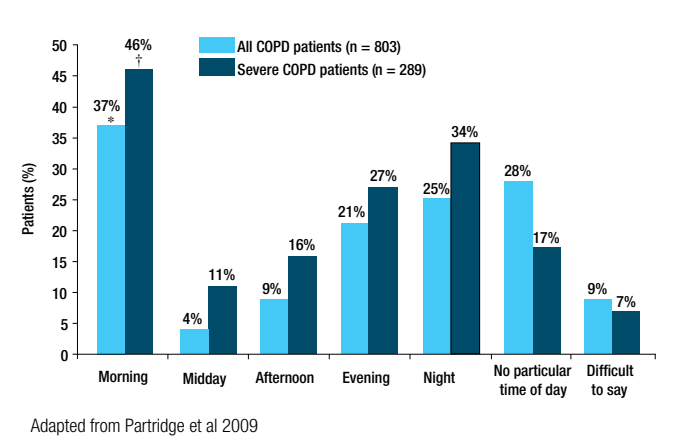
The combination of a fixed-dose ICS/LABA and long-acting muscarinic antagonist (LAMA) improves lung function and reduces exacerbations compared with ICS/LABA or LAMA monotherapy in patients with exacerbations and moderate to very severe COPD.[1]

In the setting of triple therapy, in COPD patients with an FEV1 ≤50% and a history of exacerbations requiring systemic corticosteroids and/or antibiotics, budesonide/eformoterol added to tiotropium significantly reduced the rate of severe COPD exacerbations by 62% (p<0.001) and hospitalisations/ED visits by 65% (p=0.011) versus tiotropium alone in a double-blind RCT.[11] Similarly, in an open-label RCT of patients with severe or very severe COPD, budesonide/eformoterol added to tiotropium reduced the COPD exacerbation rate by 40.7% (p=0.0032) and prolonged the time to first exacerbation by 38.6% (p=0.017) versus tiotropium alone.[12]

In contrast, the addition of fluticasone propionate/salmeterol to tiotropium therapy did not result in a statistically significant reduction in the rate of COPD exacerbations in patients with moderate to severe COPD in a double-blind RCT,[13] although in this study >40% of patients in the tiotropium/placebo arm and tiotropium/salmeterol arm discontinued therapy prematurely and many crossed over to open-label ICS or LABA. It did, however, result in statistically significant improvements in lung function, quality of life, and hospitalisation rates.[13]

Morning symptoms

It is well recognised that COPD symptoms are at their worst in the mornings and that morning symptoms adversely affect the morning routine of patients with COPD.[14] In a quantitative internet survey, statistically significantly more COPD patients reported that their symptoms were more severe than usual in the morning than at other times of the day (**Figure 1**).[15] Additionally, significantly (p=0.002) more patients with severe COPD reported that their symptoms were worse than usual in the morning than at other times of the day compared with patients who had non-severe disease. Most patients (74% of all COPD patients and 96% of severe COPD patients) reported that it took longer to complete their morning routine than it used to. Shortness of breath, the most commonly reported symptom, correlated strongly with difficulties experienced with morning activities.[15]



Adapted from Partridge et al 2009

Figure 1. Time when COPD symptoms are worse than usual according to an internet survey of patients with COPD.[15] *p<0.001 versus 'midday', 'afternoon', 'evening', 'night', and 'difficult to say' groups; and p=0.006 versus 'no particular time of day' (all COPD patients); †p<0.001 versus 'midday' (severe COPD patients),

Two double-blind RCTs have assessed the effects of budesonide/eformoterol on morning symptoms and activities. In one of these studies, budesonide/eformoterol provided small but statistically significantly greater improvements in the ability to perform morning activities versus fluticasone propionate/salmeterol.[16] In the other study, budesonide/eformoterol added to tiotropium resulted in statistically significantly greater improvements in morning symptoms and morning activities compared with tiotropium alone.[11] The eformoterol component of budesonide/eformoterol has a faster onset of action than the salmeterol component of fluticasone propionate/salmeterol and also when added to tiotropium compared with tiotropium alone, which produced greater improvements in morning lung function.[11,16] This is likely to have contributed to the greater ability of patients in both studies to perform morning activities.

Pneumonia risk

Long-term COPD studies indicate that patients treated with an ICS have higher rates of pneumonia than those treated with placebo,[17] hence raising concerns that the use of ICS in COPD patients may increase their risk of developing pneumonia. Indeed, the GOLD guidelines state that the regular use of ICS raises the risk of pneumonia, particularly in patients with severe COPD.[1] However, a large pooled analysis of RCTs did not find a statistically significant increase in the risk of pneumonia associated with budesonide-containing treatments versus non-budesonide-containing treatments in COPD patients, but could not exclude a small increase in risk with budesonide-containing treatment.[18]

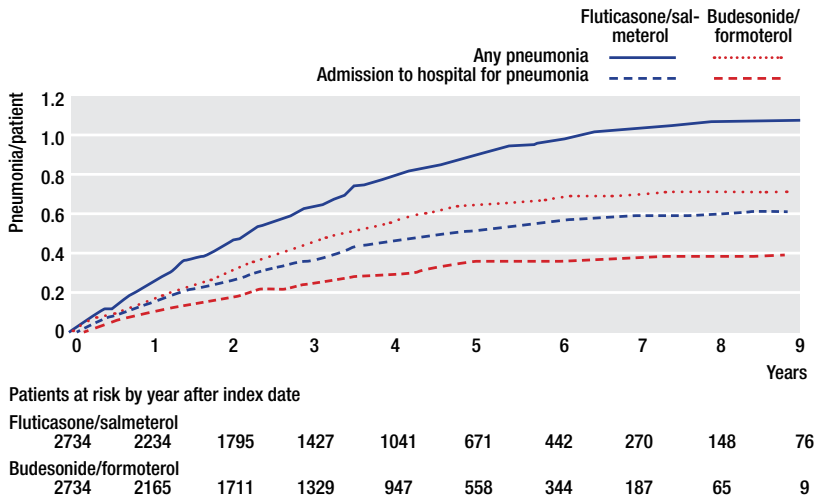
In a matched cohort study (see **Study Summary**), which looked at pneumonia and pneumonia-related mortality in COPD patients, patients treated with fluticasone propionate in general practice were statistically significantly more likely to develop pneumonia, and had a higher mortality related to pneumonia, than patients treated with budesonide.[22] A possible explanation for a higher pneumonia risk associated with fluticasone propionate treatment compared with budesonide is that fluticasone propionate causes greater local immunosuppression in the airways, which may be due, at least partially, to a longer presence of fluticasone propionate in airway epithelial lining fluid.[19]

Pneumonia and pneumonia related mortality in patients with COPD treated with fixed combinations of inhaled corticosteroid and long acting β2 agonist: observational matched cohort study (PATHOS)[22]

Authors: Janson C et al.

Methods: This propensity score-matched, population-based, retrospective, observational cohort study compared pneumonia exacerbation rates in primary care patients with COPD treated with budesonide/eformoterol (B/F) and fluticasone propionate/salmeterol (F/S). Data from primary care medical records were linked to hospital, drug, and cause of death registry data. Pairwise (1:1) propensity score matching was carried out at the index date (first prescription) by prescribed ICS/LABA. Hospitalisations, ED visits, and collection of oral corticosteroids or antibiotics for COPD constituted exacerbations.

Results: A total of 9,893 patients (mean age 67 years) had a record of ICS/LABA therapy following COPD diagnosis and were eligible for pairwise matching (7,155 B/F and 2,738 F/S), which yielded two cohorts of 2734 patients. During the study period, 2115 (39%) of these patients had ≥1 recorded episode of pneumonia, with 2746 episodes recorded during 19,170 patient years of follow up. The pneumonia rate was 73% higher in patients treated with F/S compared with B/F (rate ratio 1.73; 95%CI: 1.57–1.90; p<0.001). Similarly, admission to hospital related to pneumonia was 74% higher in patients treated with F/S compared with B/F (rate ratio 1.74; CI: 1.56–1.94; p<0.001). The cumulative number of pneumonia events admissions to hospital showed a uniform pattern over time (**Figure 2**). The incidence of pneumonia increased in both treatment groups with increasing disease burden but was higher with F/S treatment. Additionally, there was a 76% higher risk of pneumonia-related mortality in patients treated with F/S compared with B/F (hazard ratio 1.76; 95% CI: 1.22–2.53; p=0.003).



Adapted from Janson et al 2013

Figure 2. Cumulative number of pneumonia events and admissions to hospital related to pneumonia per patient over a 9-year period.[22]

Comment: This observational retrospective matched cohort (real-world) study gives the best evidence thus far that the increased risk of pneumonia associated with inhaled corticosteroid use may not be a class effect but may vary between different corticosteroids. The potential confounders were adjusted for using propensity scores and there was a small but clear difference between budesonide and fluticasone propionate. One limitation is that the definitions of COPD and pneumonia were by clinical documentation rather than by spirometry, radiology, or laboratory data. Importantly, those in the budesonide/formoterol group had lower rates of hospital admission and mortality related to pneumonia although there was no difference in the overall risk of death between the groups. Moreover, the between-treatment difference was most marked in patients at higher risk for pneumonia. While there is a possibility that the difference in outcome here is due to differences between patients rather than the medications, the clinician should bear these findings in mind when considering inhaled therapy in patients at high risk of pneumonia.

Predicting exacerbation risk and treatment response

Peripheral blood eosinophil count might help to identify COPD patients who will experience fewer exacerbations when taking ICS. Post-hoc analyses of previous clinical trials have demonstrated differences in exacerbation rates between patients treated with ICS who have high eosinophil counts and those who have low eosinophil counts.[23] However, these analyses were limited by the selection of arbitrary eosinophil count cut-off values and variation among the analyses in the use of relative or absolute eosinophil counts.[23]

More recently, a novel analysis (see **Study Summary**) has evaluated the relationship between blood eosinophil count and the treatment benefit of ICS across the entire measured blood eosinophil count range, rather than using arbitrary cut-off values.[23] This post-hoc pooled analysis investigated the clinical effect (determined from exacerbation rates, lung function, and quality of life) of budesonide/eformoterol in patients with COPD modelled by blood eosinophil count at study entry. The results suggest that an increased blood eosinophil count may be predictive of a higher exacerbation risk in COPD patients with a history of previous exacerbations who are not receiving ICS. The results also suggest that budesonide/eformoterol may substantially reduce the risk of exacerbation compared with eformoterol alone over the measured blood eosinophil range. Therefore, for many patients with COPD and a history of exacerbations, there is potential clinical benefit from budesonide/eformoterol and that this potential benefit can be identified by measuring the blood eosinophil count.

Predictors of exacerbation risk and response to budesonide in patients with chronic obstructive pulmonary disease: a post-hoc analysis of three randomised trials[23]

Authors: Bafadhel M et al.

Methods: This post-hoc analysis pooled data from three RCTs of budesonide/eformoterol in patients with COPD and a history of exacerbations for whom baseline blood eosinophil counts were available. Eosinophil count was modelled as a continuous variable to identify the characteristics that determine exacerbation risk and clinical response to ICS.

Results: Data from 4528 patients with moderate to severe COPD and a history of exacerbations requiring systemic corticosteroids and/or antibiotics was included in the pooled analysis. In patients receiving eformoterol alone, increased eosinophil count was associated with increased exacerbations. The first occurrence of a significant treatment effect of budesonide/eformoterol 160/4.5 μg was at an eosinophil count of 0.10 x 10^9 cells/L ($p_{interaction}$<0.001). Further interactions between treatment effects of budesonide/eformoterol over eformoterol and eosinophil count were also noted in symptoms scores (the St George's Respiratory Questionnaire [$p_{interaction}$=0.0043]) and pre-bronchodilator FEV_1 (linear effect p<0.0001, $p_{interaction}$=0.067). Only eosinophil count and smoking history had a significant interaction with budesonide/eformoterol 160/4.5μg as independent predictors of response to budesonide/eformoterol in terms of reducing exacerbations.

Comment: This study found that higher blood eosinophil counts could be used to predict a greater risk of future exacerbations and are associated with reduced exacerbations when treated with budesonide/eformoterol compared with eformoterol alone. There is accumulating evidence for using the eosinophil count to guide treatment in obstructive lung diseases. This study suggests that blood eosinophil count can help guide when inhaled corticosteroids may be introduced with a favourable risk-benefit ratio and that a low blood eosinophil count may be used as a "rule out" test and prevent unnecessary prescriptions where the risk-benefit ratio is less favourable. Unfortunately, the rates of pneumonia and hospitalisation for pneumonia were not part of the available data set as this is a post-hoc analysis of a pooled population.

EXPERT'S CONCLUDING COMMENTS

Both real-world studies as well as traditional RCTs are helpful to guide clinicians in tailoring treatment for individual patients. Whilst traditional RCTs may be more scientifically rigorous and tightly controlled, real-world studies offer more accurate reflections of real patients, difficulties in treatment, and clinical practice. Budesonide/eformoterol has been shown to be efficacious in reducing COPD exacerbations, improving symptoms and activity scores, and is a useful adjunct to a long-acting muscarinic agent. There is an evolving evidence base in the use of eosinophils to guide inhaled corticosteroid treatment in this population although further work is still needed to develop a "prescription tool" to help inform clinicians at which point the benefit of symptom improvement and reduction of exacerbations outweigh the increased risk of pneumonia in individual patients.

TAKE-HOME MESSAGES

- Real-world studies, which better reflect usual community care than RCTs, indicate that budesonide/eformoterol is associated with greater reductions in exacerbations leading to hospitalisations and ED visits than fluticasone propionate/salmeterol in patients with COPD.
- COPD symptoms are at their worst in the mornings and morning symptoms adversely affect the morning routine of COPD patients.
- Evidence from RCTs suggests that budesonide/eformoterol provides greater improvement in morning symptoms and activities than fluticasone propionate/salmeterol and when added to tiotropium (triple therapy) compared with tiotropium alone in patients with COPD.
- Evidence from RCTs also indicates that budesonide/eformoterol added to tiotropium (triple therapy) is more effective than tiotropium alone in reducing the rate of COPD exacerbations in patients with moderate to very severe COPD.
- A post-hoc pooled analysis of three RCTs in patients with moderate to severe COPD treated with budesonide/eformoterol suggests that blood eosinophil count predicts exacerbation risk and clinical response to ICS.

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