



JOURNAL CLUB

SEPTEMBER 2018 | KEY PAPER SUMMARIES

Cost-effectiveness of roflumilast as an add-on to triple inhaled therapy versus triple inhaled therapy in patients with severe and very severe COPD associated with chronic bronchitis in the UK

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Int J Chron Obstruct Pulmon Dis 2018;13:2707-2720

doi: 10.2147/COPD.S167730

Patients with COPD are prone to disease exacerbations, which can have significant impact on their health. Patients with COPD are commonly treated with triple inhaled therapy, which consists of ICS, LABAs and LAMAs. However, exacerbations can persist despite treatment. Roflumilast is a phosphodiesterase type four inhibitor that can be added to triple inhaled therapy to further reduce the risk of exacerbation.

In this study, researchers assessed the lifetime costs, outcomes and cost-effectiveness of adding roflumilast to triple inhaled therapy (triple inhaled therapy + roflumilast) in patients with severe and very severe COPD (defined as FEV₁ <50%). The primary endpoint was the reduction in the rate of moderate to severe COPD exacerbations. In addition to severe to very severe COPD, patients included had chronic bronchitis and were documented to have at least two moderate or severe exacerbations in the past year. Data were collected from previous roflumilast trials, REACT and RE²SPOND.

Results demonstrated a non-significant reduction in the rate of moderate or severe exacerbations in patients treated with the triple inhaled therapy + roflumilast compared with those treated with triple inhaled therapy alone. Based on the calculated costs, the triple inhaled therapy + roflumilast group demonstrated an additional 0.14 QALYs at an incremental cost of £3,508, generating a deterministic incremental cost-effectiveness ratio of £24,976.

Researchers concluded that, compared with triple inhaled therapy alone, roflumilast is a cost-effective add-on treatment in patients with severe to very severe COPD, chronic bronchitis and a history of exacerbations. Based on these findings, the NICE updated its guidance to now recommend the use of roflumilast as an add-on to triple inhaled therapy for patients with severe COPD and a history of ≥2 exacerbations in the previous year despite previous treatment.

This study was funded by AstraZeneca UK Ltd.

Adverse outcomes from initiation of systemic corticosteroids for asthma: long-term observational study

David Price, Frank Trudo, Jaco Voorham, et al.

J Asthma Allergy 2018;11:193-204

doi:10.2147/JAA.S176026

Patients with respiratory conditions are commonly prescribed SCS, which are also used to treat or reduce the risk of flare-ups of inflammatory conditions, such as rheumatological and autoimmune diseases, allergic reactions and inflammatory bowel disease. Their maintenance use raises concerns regarding increased risk of infections and cardiovascular events, type 2 diabetes mellitus, osteoporosis, cataracts, weight gain, insomnia, depression and behavioural disturbances. Even short-term use of OCS is associated with increased rates of sepsis, thromboembolism and fracture within 30 days of OCS initiation.

SCS are a mainstay of treatment for asthma exacerbations, and are often prescribed as part of a daily maintenance therapy for patients with severe asthma.

In this long-term, observational study of a broad population of patients with active asthma of all levels of severity, Price and colleagues set out to investigate the impact of initiating SCS (and of SCS exposure) on known SCS-associated adverse outcomes.

Using anonymised, longitudinal medical record data, the historical matched cohort study of patients (n = 307,213) with active asthma compared those initiating SCS with those not exposed to SCS, and comprised a minimum one-year baseline period and a minimum two-year follow-up period. Patients were at least 18 years of age with no less than three years-worth of continuous practice records.

The study findings, in a broad asthma population initiating SCS, including both acute and maintenance SCS, and followed over a median exposure period of more than seven years, indicate that increasing cumulative exposure and increasing mean daily exposure to SCS places patients at a high risk of potentially life-changing SCS-related adverse outcomes, which have a substantial financial impact on the health system. This finding is both statistically and clinically important, as increased risks of adverse outcomes were seen at relatively low cumulative and mean daily SCS exposures.

An important practical implication of this finding is that patients should be evaluated and considered for alternative treatment strategies in the course of their asthma to avoid the need of OCS.

This study was funded by AstraZeneca.

Temporal transitions in COPD severity stages within the GOLD 2017 classification system

Joan Soriano, Michael Hahsler, Cecilia Soriano, et al.

Respir Med 2018;142:81-85

doi:10.1016/j.rmed.2018.07.019

The diagnosis and staging of COPD is controversial. At the end of 2016, the GOLD modified its global COPD severity staging recommendations, to be based on symptoms and history of exacerbations exclusively, and not including FEV₁. However, the stability of the new staging is unknown, as is the frequency of the individual transitions in COPD severity beyond one year.

The objective of this study was to determine the longer-term distribution (longer than one year and up to five years) of the GOLD COPD stage transitions.

Soriano and colleagues analysed data from the CHAIN study, a multicentre, observational, prospective cohort of COPD patients. They investigated 959 COPD patients with a mean age of 66.3 years, of whom 19% were female and 33.3% were smokers. At baseline, their severity was distributed (according to GOLD criteria) as 37.7% A, 38.3% B, 8.2% C and 15.7% D. Participants were followed up over the five-year study period, with clinic visits every 12 months and telephone interviews every six. The recruitment period ran from January 2010 to March 2012. A Markov chain model was created and analysed, in which the probability of an event is dependent solely on the state attained in the previous event.

Although its novelty, size and length of follow-up represented study strengths, the investigators noted its limitations. As an

observational, non-interventional study, there were determinants that may have had a role in the observed stage transitions, for example, smoking cessation and adherence/variability in COPD pharmacotherapy. Also, over the course of five years the cohort size had shrunk to 388 patients (38.2% of baseline).

The authors observed that, although the proportions of all stages remained largely stable in the overall population after baseline assessment (from A being the most frequent, to B, D and then C as the least frequent), there were significant changes between stages at the individual patient level, especially for the more severe stages, up to five years of follow-up.

The CHAIN study was funded by AstraZeneca Spain S.A.

Clinical characteristics and medication patterns in patients with COPD prior to initiation of triple therapy with ICS/LAMA/LABA: A retrospective study

Michael Bogart, Richard H Stanford, Tyler Reinsch, et al.
Respir Med 2018;142:73–80
doi:10.1016/j.rmed.2018.07.009

Long-acting bronchodilation with a LAMA, LABA or combination of the two is the foundation of COPD pharmacological treatment. For some patients, however, this is not enough, and symptom burden or risk of exacerbation drive the escalation to multiple bronchodilators plus an ICS. Triple therapy with ICS/LAMA/LABA is currently recommended for patients taking bronchodilator therapy with persistent symptoms or who are at high risk for future exacerbations.

This retrospective study identified patients with a diagnosis of COPD from a US health insurance database between January 2014 and March 2016. The 'index date' was the first appearance in the patient's record of a dispensing overlap of the three drug classes (ICS, LABA and LAMA), which completed the triple therapy combination. A total of 69,743 patients were initially identified; after applying inclusion and exclusion criteria, 13,701 patients were considered first-time users of triple therapy and their records further examined.

Nearly all patients – 95.7% – initiated triple therapy using a LAMA and a fixed-dose ICS/LABA inhaler. The number of patients with prescriptions for one or two medication classes increased in the time period leading up to the index date.

More than half (59.8%) of patients had at least one moderate or severe exacerbation during the study period, and 6.4% had a severe exacerbation. Only 9.6% of patients initiated triple therapy as their first treatment, i.e. without having been treated with an ICS, LABA or LAMA, or experienced an exacerbation, during the baseline period.

In conclusion, the results of this study indicate that most patients receiving triple therapy did so after prior treatment with at least one maintenance medication, or after a moderate or severe exacerbation, in line with current treatment guidelines. Limitations in the study data do not permit further analysis of the 9.6% who started immediately on triple therapy, but the authors postulate this could have been due to persistent patient-reported symptoms, mild exacerbations or spirometry findings.

This study was funded by GlaxoSmithKline.

Exercise-induced bronchoconstriction: prevalence, pathophysiology, patient impact, diagnosis and management

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npj Prim Care Respir Med 2018;28:31
doi:10.1038/s41533-018-0098-2

EIB was previously known as exercise-induced asthma or exercise-induced bronchospasm, before being named EIB in 1970. It is defined as acute, transient, reversible airway narrowing, occurring during or soon after exercise. Most cases occur in patients with asthma, but EIB has also been experienced by individuals without asthma, including some elite athletes.

EIB is estimated to occur in approximately 90% of people with asthma, and is more likely to manifest in patients with poorly controlled asthma. The prevalence in the general population is estimated at 5–20%, but few population studies differentiate between patients with asthma and those without. The prevalence in children is generally higher, at 3–35%, and those living in urban environments are 1.6 times more likely to experience EIB than those in more rural areas. High-performance athletes are also at increased risk, due to prolonged inhalation of cold, dry air and airborne pollutants. Among elite or Olympic-level athletes, the prevalence of EIB has been estimated at 30–70%.

Present theories suggest that hyperventilation during exercise leads to water loss via evaporation, dehydrating the airway surfaces and initiating the mast cell-mediated signalling cascade, which results in the contraction of bronchial smooth muscle. Breathing cold air further increases the dehydration effect, and therefore athletes performing in cold weather conditions demonstrate the highest rates of EIB.

Unless well managed, EIB can limit patients' ability to exercise, depriving them of the well-known health benefits of regular exercise. In patients without asthma, non-pharmacological treatments for EIB include pre-warming and humidifying air during exercise (e.g. by breathing through a face mask) and utilising a warm-up period. If symptoms continue, use of short-acting beta-agonists, leukotriene receptor antagonists or chromones should be considered. In patients with asthma, EIB may indicate poor asthma control, and therefore attention should be focused on optimising asthma management.

Abbreviations/acronyms:

COPD = chronic obstructive pulmonary disease
EIB = exercise-induced bronchoconstriction
FEV₁ = forced expiratory volume in one second
GOLD = Global Initiative for Chronic Obstructive Lung Disease
ICS = inhaled corticosteroids
LABA = long-acting beta-2 agonist
LAMA = long-acting muscarinic antagonist
NICE = National Institute for Health and Care Excellence
OCS = oral corticosteroids
SCS = systemic corticosteroids



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