Thomas Jones

Tom.jones@doctors.org.uk
@TLJ23
https://www.linkedin.com/in/thomasjones0/

Journal club

Initial inhaler choice in COPD: real-world evidence

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Commentary on:

Suissa S, *et al*. Comparative effectiveness of LABA-ICS *versus* LAMA as initial treatment in COPD targeted by blood eosinophils: a population-based cohort study. *Lancet Respir Med* 2018; 6: 855–862.

Context

Long-acting bronchodilators are the mainstay of inhaled therapy in COPD. Both long-acting β-agonists (LABA) and long-acting muscarinic antagonists (LAMA) are effective at reducing breathlessness and exacerbation frequency, with LAMA being the more effective of the two classes [1]. The Global Initiative for Chronic Obstructive Lung Disease advises that inhaled corticosteroids (ICS) are reserved for those who exacerbate more frequently and preferably after the addition of dual long-acting bronchodilators [2]. Some people with COPD benefit from ICS, and there is evidence that blood eosinophil count is a useful biomarker to highlight who might benefit [3]. ICS are known to increase the risk of pneumonia in people with COPD [4] but despite the guidelines, many people with COPD are prescribed LABA/ICS combinations as initial inhaled therapy [5]. Suissa *et al*. [6] reported real-world evidence comparing LABA/ICS with LAMA as the initial treatment of COPD, stratified by blood eosinophil count, detailing both the benefits for exacerbation frequency and risk of pneumonia with each treatment strategy.

Methods

Suissa *et al*. [6] used the UK Clinical Practice Research Datalink (CPRD) (https://www.cprd.com/), which comprises anonymised primary care data from >10 million people, collected and coded using Vision Healthcare (London, UK) and EMIS Health (Leeds, UK) general practice data systems. These were linked to the Hospital Episode Statistics (HES) database [7] to collect data on hospital admissions. Suitable participants met four inclusion criteria: they were >55 years of age, had a peripheral blood eosinophil count measured prior to entry, were coded as having COPD, and started either LABA/ICS or LAMA between 2002 and 2015. Data were analysed for up to 12 months from the initial prescription. The primary outcome measure was a severe or moderate exacerbation, defined as a hospital admission for COPD or a new prescription of prednisolone respectively. High-dimensional propensity scoring was used to match each participant initiating LABA/ICS with one initiating LAMA. Stratification was performed by blood eosinophil count using thresholds of <2%, 2–4% and >4%.

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In a real-world cohort (UK's CPRD), initiating inhaled treatment for COPD with ICS/LABA rather than LAMA improves exacerbation rate without significant increases in pneumonia rates in those with peripheral blood eosinophil counts >4% http://bit.ly/2OZpij5

Main results

A total of 32370 suitable participants were initially identified, giving groups of 12366 each once participants had been paired. The LABA/ICS group predominantly received fluticasone and salmeterol while 99.9% of the LAMA prescribed were tiotropium. The groups were well matched in terms of age, sex and exacerbation history but current smokers were more likely to receive a LAMA, while those with a history of asthma were more likely to receive LABA/ICS.

Overall, there was no difference in the rate of moderate or severe exacerbation between the groups. The LABA/ICS group had an adjusted hazard ratio (HR) of 0.95 (95% CI 0.90–1.01) compared to the LAMA group, and this was confirmed in the stratified analysis by HRs of 1.03 and 1.00 in the <2% and 2–4% eosinophils strata. The high eosinophil stratum, however, had a reduced HR of 0.79 (95% CI 0.70–0.88) when given LABA/ICS. The analysis of severe exacerbations alone showed a similar pattern, with a nonsignificant trend towards increased exacerbations for LABA/ICS in the low eosinophil stratum (HR 1.14 (95% CI 0.88–1.46) but a significant reduction in the high eosinophil stratum with an HR of 0.67 (95% CI 0.48–0.92).

Participants with two or more exacerbations per year benefitted from LABA/ICS more than LAMA (HR 0.87, 95% CI 0.79–0.97) but again, this was mainly due to the effect size in the stratum with >4% eosinophils (HR 0.78, 95% CI 0.63–0.97).

Pneumonia rates were, as expected, increased in the LABA/ICS group overall, with an adjusted HR of 1.37. This was driven by increased HRs in the <2% and 2–4% strata, but the most eosinophilic stratum (>4%) did not show a significantly increased rate of pneumonia

Commentary

In agreement with previous studies [8–10], this paper confirms that peripheral blood eosinophil count can be used to select people with COPD who benefit from ICS, in this case in combination with a LABA. It also confirms that LABA/ICS is associated with an increased risk of pneumonia [4], but that this does not appear to be the case for those with eosinophilia >4%. Overall this shows that COPD patients with peripheral blood eosinophilia have more benefit and less risk from LABA/ICS combination inhalers than the general COPD population.

The advantages of this study include the very large number of participants included, with >12000 in each group, and the real-world nature of the data. These data carry the normal caveats applied to observational cohorts; in this case, reliance on disease coding and the lack of specific exclusion of those with asthma being particularly relevant. Inhaled steroids are the mainstay of treatment for asthma, particularly in the new Global Initiative for Asthma strategy [11]. Over 43% of the LABA/ICS cohort had a previous diagnosis of asthma; late-onset asthma is a common problem and no spirometric or smoking criteria were used for inclusion so the incorporation of a significant number of people whose primary problem was asthma rather than COPD cannot be ruled out. The follow-up was limited to 12 months following the prescription.

While LABA/ICS were significantly better at preventing exacerbations than LAMA in those with raised blood eosinophils, the reverse was not true in those in the lowest eosinophil group despite previous evidence to suggest it should be [1]. This may be due to the selection of participants for the randomised controlled trials on which the previous data were based or lack of data for the selection of participants in this study.

A contradictory study, also based on the CPRD, was published in *COPD* this year, which showed that withdrawal of ICS in 48157 participants with COPD resulted in a lower risk of moderate or severe exacerbations regardless of peripheral blood eosinophil count [12]. People with a diagnosis of asthma were excluded; however, it was not specified that the blood eosinophil measurement was taken prior to enrolment, the definition of an exacerbation was based purely on coding and the data were not linked to HES. This demonstrates the difficulty of reaching definitive conclusions using retrospective observational data, despite large the dataset.

It is common to have multiple measurements of blood counts, and variability in eosinophil levels is expected and reported [10, 13]. Data from the CPRD show that people with COPD have less stable counts but low eosinophil counts are more stable [14]. In this study, a sensitivity analysis was conducted in which participants with two blood eosinophil measurements were placed in the 2–4% group unless both of their measurements were <2% or >4%. This did not affect the results, although grouping more participants into the middle stratum might not be expected to alter the results. There is no current consensus on how best to classify peripheral blood eosinophil counts; classification may be absolute (*e.g.* 400 cells per µL) or relative (4%), thresholds vary in the literature (2%, 4%, 150 cells per µL, 300 cells per µL, *etc.*) and multiple measurements are taken so the value used could be the highest, the average or the most recent.

Overall, despite the limits of retrospective cohort studies, this paper helps to confirm that people with COPD and peripheral blood eosinophilia benefit from inhaled steroid in their inhaled treatment regimen. Those with lower eosinophil count are less likely to benefit and are more likely to have an increased risk of pneumonia if ICS are given.

Implications for practice

LABA/ICS may be preferable to a LAMA as initial therapy for patients with COPD with a raised peripheral blood eosinophil count of ≥4% as it may be associated with an improvement in moderate to severe exacerbation frequency without a significant increase in the risk of pneumonia. This study again highlights the value of the peripheral blood eosinophil count as a low-cost test that provides benefit when choosing inhaled therapy in COPD. Many people being started on inhaled therapy are likely to have had an eosinophil count at some point and reviewing this may aid decision making over the initial treatment.

Affiliations

Thomas Jones

Dept of Respiratory Medicine, Portsmouth Hospitals NHS Trust, and Faculty of Science, University of Portsmouth, Portsmouth, UK.

Conflict of interest

T. Jones reports personal fees and nonfinancial support from Chiesi Farmaceutici, and nonfinancial support from Teva, outside the submitted work.

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