

## Who is a Candidate for Inhaled Corticosteroids in Patients with COPD? - The Viewpoint of Patient-Reported Outcomes

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### Abstract

In clinical practice with patients with chronic obstructive disease (COPD), clinicians should consider patients symptoms and health status, or quality of life, which are evaluated with patient-reported outcomes (PROs). Combination bronchodilators proved to be more effective about PROs than monotherapy. Inhaled corticosteroid (ICS) is associated with risk of pneumonia in COPD patients. Adding ICS to combination bronchodilators, so-called triple therapy could be effective on dyspnea and health status in patients with elevated blood eosinophil counts. Therefore, clinicians are advised to assess and re-assess COPD patients in order to get benefits of pharmacological therapy and reduce risks of adverse events while referring to eosinophil counts.

**Keywords** Chronic Obstructive Pulmonary Disease (COPD); Patient-Reported Outcomes (PROs); Inhaled corticosteroids; Eosinophilia

### Introduction

In clinical practice of patients with chronic obstructive pulmonary disease (COPD), clinicians aim to relieve patients' dyspnoea and improve their quality of life (QOL). In fact, the Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Lung Disease (GOLD) 2019 report adopted dyspnoea level measured by modified MRC dyspnoea scale and QOL, or health status, evaluated by COPD Assessment Test (CAT) as vital information which will determine first-line pharmacological treatment [1] and most randomized trials of treatment on its efficacy include either evaluations of dyspnoea or health status or both, which are important patient-reported outcomes (PROs).

As for therapy for relieving dyspnoea and improving health status in outpatient management, key drugs are inhaled bronchodilators (long-acting muscarinic receptor antagonists (LAMA), long-acting beta<sub>2</sub> agonists (LABA), combinations of LAMA and LABA). In addition to bronchodilators, role of inhaled corticosteroids (ICS) has been repeatedly discussed over three decades [2-5]. It has been considered that ICS may be administrated mainly for preventing acute exacerbations but introducing single-inhaler triple therapy (LAMA/LABA/ICS) into practice could bring new perspectives on efficacy of PROs [6].

### Literature Review

In this article, we would like to review published data focusing on results of PROs. The aim of this review is clarifying the role of ICS in the management of symptoms and health status and demonstrate who are likely to get benefit of ICS and who are not.

### Patient-Reported Outcomes (PROs)

While quality of life is the subjective perception of the impact of health, with a self-determined evaluation of how satisfactory the relevant components of one's life are, the term "health status" is a group measurement which it works as a standardized tool for detecting the impact of many diseases while quality of life is the subjective perception of the impact of health, with a self-determined evaluation of how satisfactory the relevant components of one's life are. Although the term quality of life is often used interchangeably with the term health status, it is likely that health status should be preferred in this situation.

Most randomized trials on evaluating medical interventions to COPD include outcomes on dyspnoea and health status, which are often mentioned as patient-reported outcomes (PROs). When interpreting results of PROs, it should be recognized how many scores each measurement shows as clinically significant threshold or minimal clinically important difference (MCID) [7].

Most widely used clinical dyspnea rating is Baseline Dyspnea Index (BDI) and Traditional Dyspnea Index (TDI) [8]. The BDI, which suits for cross-sectional analyses, recognizes five grades for each of the following categories: functional impairment, magnitude of task, and magnitude of effort and scores from 0 and 12. The TDI enables us to evaluate changes in dyspnea level with scoring -9 to +9. The authors demonstrated that the MCID of the TDI is one unit [9].

Regarding health status measures, the St. George's Respiratory Questionnaire (SGRQ) comes first [10]. The SGRQ has the following three components: Symptoms, which reflects the respiratory symptoms; Activity, which reflects the activities that evoke or are limited by dyspnea; and Impact, a measure of the overall disturbance. The total score of the SGRQ was also calculated. The SGRQ scores ranged from 0 to 100, with 0 indicating no impairment in the health status. The developers proved the MCID of SGRQ as around 4 units [11]. Some studies evaluate patients whose improvements from

baseline of 4 units grouped as SGRQ responders. CAT is also one of the health status measures and has similar characteristics to the SGRQ.

### Mono versus dual bronchodilators

Before getting into ICS, it might be helpful for readers to recognize efficacy of bronchodilators on PROs of COPD patients. Several studies on representative drugs have shown that combination bronchodilators are more effective on PROs compared to monotherapies [12-14]. It is of interest to note that these three studies similarly demonstrated dual bronchodilators had significantly greater improvement of TDI and SGRQ compared to individual monotherapy and placebo, but those improvements exceeded the MCID only against placebo, not against monotherapy. In another way of interpreting results, three studies claimed that rates of responders who had changes in scores more than the MCID were more likely to find in patients with the dual bronchodilators than with its individual mono bronchodilators.

Then who are likely to get benefits out of receiving dual bronchodilators? Martinez clearly showed that patients with a greater symptom burden measured with CAT had significant improvements of the SGRQ [15]. This suggest a better clinical benefit from combination bronchodilators in symptomatic patients than in patients without symptoms. Therefore, in daily clinical practice, clinicians are advised to use combination bronchodilators with assessment and re-assessment as shown management cycle, which consists of review, assess, and adjust, in GOLD 2019 [1].

### Single inhaler triple therapy and their efficacy on PROs

As of the present moment (Oct 2019), three single triple inhalers (ICS/LABA/LAMA) have been introduced into clinical practice [16,17]. With regards to efficacy on PROs, one randomized clinical trial reported COPD patients with single inhaler triple therapy had greater benefits on the SGRQ scores compared to monotherapy of LAMA [17], and two trials demonstrated better outcomes of TDI and SGRQ in patients with triple therapy compared with LAMA/LABA combination therapy [16].

Yet looking further into latter two studies would be helpful for clinicians. Lipson et al. evaluated triple therapy in comparisons with two combination therapies, ICS/LABA and LAMA/LABA [6]. To illustrate efficacy of add-on ICS, here were the results of SGRQ scores of triple therapy and LAMA/LABA. Both patient groups showed significant changes and exceeded the MCID of SGRQ; mean change of baseline were -5.5 and -3.7, respectively. Difference between two groups, however, was only -1.8, insufficient for clinically meaningful scores. In addition, triple therapy produced SGRQ responders of 42% whereas LAMA/LABA did those who of 34%.

Another study from Ferguson et al. compared triple therapy with ICS/LABA and LAMA/LABA [16]. In their results, patients with triple therapy and LAMA/LABA showed 1.25 and 1.07 in TDI score, respectively, which are more than the MCID of TDI. As for the SGRQ scores, both groups demonstrated significant changes from baseline (-7.5 and -6.3, respectively) and exceeded the MCID. However, difference of TDI and SGRQ scores between two groups did not reach the MCID. In short, as we mentioned in the section above, triple therapy produced statistically improvements in PROs compared with LAMA/LABA therapy but failed to exceed the MCID.

These findings may lead us to consider who would get benefit of single triple inhaler rather than dual bronchodilators. Why should we

consider this? Because a Cochrane review clearly exhibited that ICS use is associated with higher prevalence of oral candidiasis, hoarseness, skin bruising and pneumonia [18]. One population-based cohort study comparing ICS/LABA versus LAMA alone showed that the increased risk of pneumonia was associated with the ICS component, especially blood eosinophilic concentrations of less than 4% [19]. This study might give important concept of precision medicine to clinical practice: level of eosinophils could be a marker for deciding pharmacological therapy, ICS/LABA or LAMA.

### Blood eosinophils and efficacy of ICS on PROs

Recent studies have demonstrated that blood eosinophil counts predict the efficacy of ICS in preventing future exacerbations [20,21]. As for PROs, Pascoe et al. demonstrated that blood eosinophil counts predict efficacy on PROs [19]. For example, at blood eosinophil counts less than 90 cells per  $\mu\text{L}$  and at counts of 310 cells per  $\mu\text{L}$  or more, the triple therapy versus LABA/LAMA treatment difference was -0.01 and 0.30 for TDI score, and -0.01 and -2.78 for SGRQ total score, respectively. They clearly demonstrated that the comparison of ICS-containing treatments with LABA/LAMA showed increasing effect sizes at higher baseline blood eosinophils counts for TDI and SGRQ score [22].

This study should be the first to prove that baseline eosinophil counts would predict efficacy of ICS-containing therapy with regard to PROs such as SGRQ and TDI. In real-world clinical practice, before initiating single triple inhaler, blood eosinophil counts should be taken into consideration.

### Discussion and Conclusion

This brief review focused on efficacy of therapies on patient-reported outcomes, such as dyspnea and health status in subjects with COPD. Many randomized studies demonstrated that certain therapies had statistically significant improvements, but occasionally failed to exceed the MCID. Regarding to ICS, while ICS is clearly related to risk of pneumonia, clinicians are advised to use eosinophil counts as a possible biomarker for expecting the efficacy. Evaluating patients with PROs would enable us to give patients benefits of therapy and reduce possibility of risk of adverse events in real-world clinical practice.

### Conflicts of Interest

The authors declare no conflict of interest.

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