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Single inhaler triple therapy in COPD – all that glitters is not gold

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Dear Editor,

The recent studies on combination triple therapy of inhaled corticosteroid, long acting beta$_2$ agonist and long-acting muscarinic antagonist (ICS-LABA-LAMA) in COPD have consistently demonstrated an improvement in exacerbation frequency and/or improvement of lung function. A *post-hoc* analysis of the IMPACT study has shown a reduction in all-cause mortality with vilanterol/umeclidinium/fluticasone furoate (VI/UMEC/FF); this is the first time when an inhaled therapy has shown mortality benefits in COPD [1]. Studies have observed rampant over-prescription of triple therapy both in primary care and in specialized COPD clinics [2]. With the recent evidence, can we rationalize our temptation to prescribe triple therapy in all COPD patients? Should single inhaler triple therapy (SITT) be the initial therapy for every COPD patient attending the pulmonology clinic?

The available evidence needs to be weighed carefully before making a decision that might require shifting of the patient to a new device and potentially increase costs to the patients.

First, it is well-known that randomized controlled trials (RCTs) maintain strict inclusion criteria and are not representative of the real-world scenario. Only 1.8%, 5.4%, and 24% of patients in TRIBUTE, IMPACT, and KRONOS would qualify for the DACCORD (a real-world observational COPD study), respectively [3]. Hence, the RCTs results could not be generalized to the majority of COPD patients in clinical practice.

Second, most patients in the SITT RCTs were already on inhaled corticosteroid (ICS) before enrollment (Table 1). *Post-hoc* analysis of the WISDOM trial indicated has increased exacerbation frequency after the withdrawal of ICS in patients with absolute eosinophil count >150 cells/mm^3 [4]. The median eosinophil counts in the patients in landmark RCTs of triple therapy were more than 150 cells/mm^3 across all arms (Table 1). Of patients randomized to long-acting muscarinic antagonist and long acting beta$_2$ agonist (LAMA-LABA) arms, 27.8%,46.2%, and 40% of patients were on ICS-LABA-LAMA before enrollment in KRONOS, ETHOS, and IMPACT trials, respectively. Except for TRIBUTE and TRINITY, ICS was permitted during the short two-week run-in period as well. After the run-in period, ICS was abruptly discontinued at randomization. Given the population characteristics, abrupt ICS withdrawal led to increased exacerbations in the LAMA-LABA arm, which might have led to a statistically significant difference in exacerbation rates between LAMA-LABA and SITT arms. The mortality benefit with VI/UMEC/FF in the IMPACT trial might be accounted for by increased exacerbations and subsequent mortality in patients in the LAMA-LABA arm after ICS withdrawal. To present an unbiased picture, it is necessary to have a subgroup analysis of patients on LAMA-LABA therapy before trial enrollment, who were shifted to triple therapy.

Third, KRONOS, ETHOS, and IMPACT excluded patients with a current diagnosis of asthma but included patients with a "past diagnosis" of asthma. Such "past asthmatics" exhibit persistent immunological changes (even in inactive disease) and been known to benefit from ICS-based inhalation therapy because of the underlying asthma component [5].

Fourth, the clinician needs to consider the MCID (Minimal Clinically Important Difference) when interpreting the trials. The average forced expiratory volume at 1 second (FEV_1) difference between the patients randomized to LAMA-LABA arm and ICS-LAMA-LABA arm in TRIBUTE and KRONOS was not significant; though the difference was statistically significant in IMPACT, the difference was not clinically significant [6]. The intergroup differences in St. George's Respiratory Questionnaire (SGRQ) between the patients receiving triple therapy and those receiving LABA-LAMA in ETHOS, TRIBUTE, IMPACT, and KRONOS were not clinically significant either. We realize that the demonstration of intergroup differences between two arms in RCT is more complicated than the demonstration of change vs. baseline. However, it is necessary to set the right clinical expectations for improvements in quality of life with SITT *vs* other available therapies.

Fifth, analysis of administrative claims in Medicare beneficiaries has demonstrated lower costs, lower exacerbation rates, and decreased incidence of pneumonia with LABA-LAMA *vs* triple

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Table 1. Landmark studies of ICS-LAMA-LABA vs LAMA-LABA in COPD.

	Formoterol/glycopyrronium /budesonide		Vilanterol/umeclidinium/ fluticasone	Formoterol/glycopyrronium/ beclomethasone
Device	pMDI with co-suspension technique		Ellipta dry powder inhaler	Extrafine formulation in pMDI
Studies	KRONOS[8]	ETHOS[8]	IMPACT[1]	TRIBUTE[8]
Duration (weeks)	26	52	52	52
Comparator arm				
ICS-LABA	✓	✓	✓	
LAMA-LABA	✓	✓	✓	✓
Others	✓ (ICS-LABA DPI)	✓ (Low dose budesonid triple therapy)		
Inclusion of Patients with past diagnosis of asthma	✓	✓	✓	Excluded patients with a diagnosis of asthma and/or past history of atopy or allergic rhinitis
Run in period				
Duration(weeks)	1-4	1-4	2	2
Medication during run-in	ICS (If previously on ICS) + Ipratropium QID	ICS (If previously on ICS) + Ipratropium QID	Unchanged	Indacaterol/glycopyyronium
% of patients on ICS based regiments prior to enrollment in each arm in the trial	TT*-72.6% ICS/LABA-71.7% LABA/LAMA-71.5%	TT-79.8%** ICS/LABA-80% LABA-LAMA-80.5% Other-81.5%	TT-71% ICS-LABA-68% LABA-LAMA-68%	TT-66% LABA-LAMA-64%
The proportion of patients previously on ICS-LABA-LAMA in each arm of the trial	TT-30.7% LAMA-LABA-27.8% ICS-LABA 34.1%	TT-46% ICS/LABA-44.4% LAMA-LABA-46.2%	TT-38% LABA-LAMA-40% ICS-LABA-38%	Patients previously on triple therapy were not eligible
The proportion of patients previously on LABA-LAMA in each arm of the trial	TT-24.3% LAMA-LABA-26.2% ICS-LABA-27.4%	TT-18.3% ICS/LABA-18.8% LAMA-LAMA-18% Other-17.2%	TT-8% LABA-LAMA-8% ICS-LABA-7%	TT-24% LAMA-LAMA-26%
Median Eosinophil count cells/mm^3 in all arms	150	165-170	160-170	230-240

*Triple therapy -ICS-LAMA-LABA; **9.6/18/320 mcg.

therapy [7]. In the current era of inflating healthcare costs across the world, it is necessary to gauge the efficacy of new and costly SITTs vs. old strategies of prescribing triple therapy (ICS-LABA+LAMA or LABA-LAMA+ICS) or LAMA-LABA in patients with COPD. Such analysis can be considered reflective of the "real-world" scenario, and guide payers and physicians.

Based on the five points described above, we propose the following action steps for clinicians regarding the prescription of SITT in COPD:

1. Before initiating patients on the newer and probably expensive SITT combinations, clinicians need to consider the right patient who would benefit from a SITT combination, depending on the inclusion criteria of the RCT of the combination under consideration.
2. COPD patients with eosinophil count >150 cells/mm^3, and/or with a history of asthma are likely to benefit from triple therapy.
3. There is no evidence to show that SITT is better than open triple therapy through different inhalers (ICS-LABA +LAMA or LABA-LAMA+ICS).
4. ICS is associated with the risk of pneumonia. Clinicians should select the lowest possible dose of ICS, as confirmed in the ETHOS study, where both doses of budesonide (320 mcg and 160 mcg budesonide) in SITT led to similar outcomes in COPD [8].

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