

Single-inhaler triple therapy utilizing the once-daily combination of fluticasone furoate, umeclidinium and vilanterol in the management of COPD: the current evidence base and future prospects

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Abstract: Maintenance pharmacological treatment for stable chronic obstructive pulmonary disease (COPD) is based on inhaled drugs, including long-acting muscarinic receptor antagonists (LAMA), long-acting β_2 -adrenoceptor agonists (LABA) and inhaled corticosteroids (ICS). Inhaled pharmacological treatment can improve patients' daily symptoms and reduce decline of pulmonary function and acute exacerbation rate. Treatment with all three inhaled drug classes is reserved for selected, more severe, patients with COPD when symptoms are not sufficiently controlled by dual LABA/LAMA therapy and exacerbations are frequent. This review focuses on the role of single-inhaler triple therapy with once-daily fluticasone furoate/umeclidinium/vilanterol fixed-dose combination, which is in phase III clinical development for maintenance treatment of severe-to-very severe COPD. In this review, we summarize evidence providing the rationale for its use in COPD and discuss the gaps to be filled in this pharmacotherapeutic area.

Keywords: COPD, fluticasone, pharmacotherapy, single-inhaler, triple therapy, umeclidinium, vilanterol

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Introduction

Chronic obstructive pulmonary disease (COPD) represents one of the most important health problems, and its prevalence in Europe has been estimated at up to 10%.¹ Between 1994 and 2010, about 2.5 million deaths in the European Union were attributed to COPD.²

Management of COPD patients mainly relies on pharmacological treatment to relieve symptoms, improve quality of life and exercise tolerance, and reduce the frequency and severity of exacerbations. Reducing COPD exacerbations is a major objective in COPD control, as they negatively affect patients' quality of life, increase the decline in lung function and represent an economic burden for society, particularly if the patient requires hospitalization.³ However, despite active research

in this pharmacotherapeutic area, there are no clinical trials showing that any existing medications for COPD modify the long-term decline in lung function that characterizes this disease.⁴ Nevertheless, analysis of the key secondary outcome in the SUMMIT study,⁵ which failed to meet its primary outcome of improvement in survival with the combination of fluticasone furoate, an inhaled corticosteroid (ICS), and vilanterol, a long-acting β_2 -adrenoceptor agonist (LABA), in COPD patients with increased cardiovascular risk, shows that fluticasone alone or in combination with vilanterol reduces the rate of forced expiratory volume in 1 s (FEV₁) decline compared with vilanterol alone or placebo without increased risk of pneumonia or cardiac adverse events.⁶

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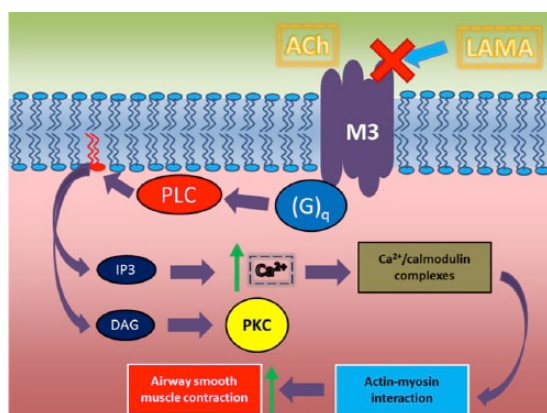


Figure 1. Signal transduction pathways following activation of muscarinic M_3 receptors by acetylcholine.

ACh, acetylcholine; DAG, diacylglycerol; $(G)_q$, GTP-binding protein; IP3, inositol-1,4,5-triphosphate; LAMA, long-acting muscarinic receptors antagonist; PKC, protein kinase C; PLC, phospholipase C.

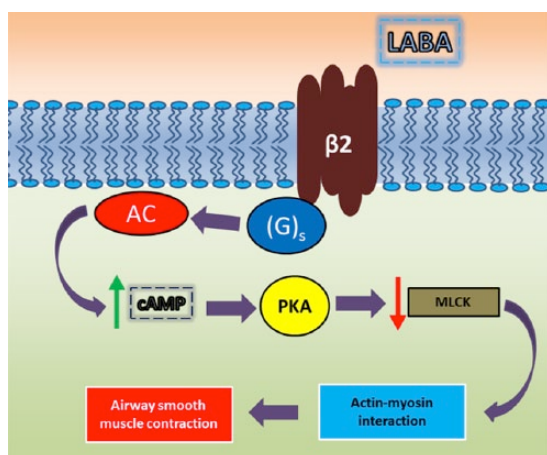


Figure 2. Signal transduction pathways following activation of β_2 adrenergic receptors by LABA.

AC, adenylyl cyclase; cAMP, cyclic adenosine monophosphate; $(G)_s$, stimulatory GTP-binding protein; LABA, long-acting β_2 -adrenoceptor agonist; MLCK, myosin light chain kinase; PKA, protein kinase A.

In this review, we summarize the current evidence and discuss future perspectives of single-inhaler therapy with once-daily fluticasone furoate/vilanterol/umeclidium in the management of COPD.

Inhaled treatment for COPD: drug classes and mechanisms of action

Classes of inhaled drugs approved for long-term treatment of COPD include long-acting

muscarinic receptor antagonists (LAMA), LABA and ICS.

LAMA-induced bronchodilation is principally due to antagonism at muscarinic acetylcholine M_3 receptors (mAChR) expressed on airway smooth muscle cells (Figure 1). M_3 receptors are coupled to guanosine triphosphate (GTP)-binding protein ($(G)_q$), resulting in an intracellular biochemical cascade that regulates intracellular calcium concentration and calcium-modulated proteins.⁷ This signaling pathway promotes actin–myosin interaction, leading to airway smooth muscle contraction. The role of M_2 receptors, expressed both at presynaptic and postsynaptic levels in airway smooth muscle cells *in vivo* is less clear. *In vitro* studies show that antagonism of presynaptic M_2 receptors increases acetylcholine release from vagal nerve endings, whereas postsynaptic M_2 receptor blockade on airway smooth muscle cells leads to increased relaxation caused by β_2 agonists.^{8,9}

As bronchodilators, LABA act *via* postsynaptic β_2 receptor activation on airway smooth muscle cells with coupling to stimulatory GTP-binding protein ($(G)_s$) and signaling that leads to reduction in contractility of airway smooth muscle through the inhibition of myosin light chain kinase (MLCK), which, in turn, promotes actin–myosin interaction (Figure 2).

The rationale for ICS use in COPD patients involves their anti-inflammatory effects. Mechanisms of action of glucocorticoids include transcription and transduction regulation of genes encoding anti-inflammatory and immune-suppressive mediators.¹⁰

Despite their effective anti-inflammatory effects, inflammation due to neutrophils and alveolar macrophages is generally resistant to glucocorticoid treatment.¹¹ By contrast, in COPD patients with peripheral eosinophilia, an ICS, in a fixed-dose combination (FDC) with a LABA, can be effective in improving clinical outcomes, particularly in terms of reduction in moderate and severe exacerbations.^{12,13}

The role of triple inhaled therapy for COPD in Global Initiative for Obstructive Lung Disease recommendations

The Global Initiative for Obstructive Lung Disease (GOLD) recommendations suggest triple

inhaled therapy with a LAMA plus a LABA plus an ICS as a step-up pharmacotherapeutic approach in COPD patients with symptoms and history of frequent exacerbations who continue to experience exacerbations notwithstanding dual LABA/LAMA therapy.^{14,15} However, evidence on the clinical benefits of triple inhaled therapy are not consistent,¹⁵ particularly regarding its effect on the COPD exacerbation rate.¹⁶ Patients in Group D of the GOLD guidelines, who are not adequately controlled with a combination of LAMA plus a LABA in terms of exacerbations, might be a target COPD population for triple ICS/LABA/LAMA. Likewise, patients who show peripheral blood eosinophil counts might benefit from ICS treatment.^{15,17}

The lack of a well-defined indication for triple ICS/LABA/LAMA therapy for COPD translates into marked differences in real-life prescription patterns.¹⁴ At present, prescription and overprescription of triple inhaled therapy seems to rely mostly on an empirical basis rather than on a rational subphenotyping approach.¹⁷

Triple inhaled therapy for COPD: evidence from prospective randomized clinical trials, systematic reviews and meta-analyses

Triple inhaled therapy for COPD might be an effective pharmacological strategy in selected COPD phenotypes, including asthma COPD overlap syndrome (ACOS), eosinophilic and frequent exacerbator phenotype, particularly when of a severe degree.^{18–20} However, further randomized clinical trials are required to clarify efficacy and define the target COPD population(s) of triple inhaled therapy. Different results have been reported according to patients' selection, follow-up duration, quality of life outcome measures, definition of COPD exacerbations and various active medications.

The CLIMB study was performed to investigate the efficacy and tolerability of budesonide/formoterol added to tiotropium compared with tiotropium alone in patients with a pre-bronchodilator FEV₁ < 50%.²¹ In this 12-week, randomized, double blind multicenter study including a total of 660 patients, improvements in lung function, morning activities, reliever use, and exacerbations rate, including severe exacerbations, were reported.²¹ Likewise, the 12-week, randomized, multicenter, open-label SECURE 1 study, including 578 patients with severe or very

severe COPD, aimed to investigate efficacy and tolerability of budesonide/formoterol added to tiotropium compared with tiotropium alone.²² Compared with monotherapy, triple inhaled therapy was associated with significant improvements in FEV₁, health-related quality of life assessed using St. George's Respiratory Questionnaire (SGRQ) and lower COPD exacerbation rates.²² In both studies, no between-group differences in adverse event rate were observed.^{21,22}

Different results were obtained with a combination of fluticasone propionate/salmeterol plus tiotropium compared to tiotropium alone.¹⁶ In a randomized, 52-week, double-blind, placebo-controlled trial including 449 patients with moderate to severe COPD comparing tiotropium plus fluticasone/salmeterol FDC, tiotropium plus salmeterol, and tiotropium alone, triple therapy did not result in a reduction in the proportion of patients who experienced a COPD exacerbation (primary outcome measure) compared with tiotropium plus placebo, although improvements in lung function, quality of life and hospitalization rate were observed.¹⁶ Similar results were reported in a 24-week, randomized, open-label, multicenter two-arm parallel study including 479 COPD patients who were treated with either fluticasone propionate/salmeterol FDC plus tiotropium or tiotropium alone.²³ Compared with tiotropium, triple therapy was associated with increased pre-bronchodilator FEV₁ from baseline to week 24 (primary outcome), whereas no between-group differences in the number of patients with COPD exacerbations were observed.²³

A meta-analysis evaluating benefits of adding fluticasone propionate/salmeterol to tiotropium showed that triple inhaled therapy was associated with a significant increase in mean change in trough FEV₁ from baseline to the end of follow up and a lower proportion of at least one COPD exacerbation compared with tiotropium monotherapy.²⁴ In the SUMMIT study, an event-driven, randomized, double-blind, placebo-controlled, parallel-group, four-arm study, including 16,485 patients with moderate COPD and increased cardiovascular risk and aiming to assess whether a single-inhaler combination of fluticasone furoate and vilanterol, could reduce all-cause mortality compared with placebo, the primary outcome was not met.⁵ However, decreased decline in FEV₁ (secondary outcome) without increased pneumonia risk was reported in the group receiving fluticasone furoate.^{6,25} These findings have potential

clinical implications for COPD management and could result in a guideline change for ICS treatment for patients with moderate COPD and increased cardiovascular risk.

A systematic review assessing the effects of the ICS and LABA combination in addition to tiotropium *versus* tiotropium alone or the combination alone in patients with COPD reported moderate-quality evidence that triple therapy reduces hospital admissions compared with tiotropium plus placebo, whereas low-quality evidence suggests that triple therapy was associated with improved disease-specific quality of life.²⁶ Compared with tiotropium alone, no significant increases in adverse effects were reported with ICS/LABA plus tiotropium.²⁶ Due to excessive variability in inclusion criteria, definition of exacerbation and follow-up duration, the effect on COPD exacerbations was heterogeneous and was not taken into consideration.²⁶

Efficacy and safety of a single-inhaler beclomethasone dipropionate/formoterol fumarate/glycopyrronium bromide FDC was evaluated in two randomized, parallel-group, double-blind, active-controlled trials: TRILOGY and TRINITY.^{24,25} The TRILOGY trial, aiming to compare efficacy of a beclomethasone/formoterol/glycopyrronium FDC in COPD patients ($n = 687$) with beclomethasone/formoterol FDC ($n = 681$), showed superiority of triple therapy over dual therapy in improving co-primary endpoints including pre-dose FEV₁, 2-h post-dose FEV₁ and transition dyspnea index (TDI) focal score at week 26.²⁷ The annualized rate of exacerbations was significantly lower in the group of COPD patients who received triple therapy, with a 23% reduction in exacerbations. No between-group differences in adverse events were reported.²⁷

In the TRINITY study, aiming to compare beclomethasone dipropionate/formoterol fumarate/glycopyrronium bromide FDC (fixed triple therapy) with beclomethasone dipropionate/formoterol fumarate plus tiotropium (open triple therapy) and tiotropium alone in COPD patients with at least one exacerbation in the previous year, a baseline post-bronchodilator FEV₁ <50% of predicted value, and a COPD assessment test score of at least 10, fixed triple therapy was superior to tiotropium alone in reducing moderate to severe exacerbation rate and noninferior to open triple therapy at 52 weeks (primary outcome). Incidence of adverse events was similar across treatments.²⁸

Fluticasone, umeclidinium and vilanterol for COPD

Umeclidinium is a potent anticholinergic agent with a prolonged duration of action in *in vitro* and *in vivo* animal models.²⁹ Once-daily umeclidinium at a dose of 62.5 µg *via* a dry powder inhaler (DPI) is approved for maintenance pharmacological treatment of COPD either alone or in an FDC with vilanterol, a LABA, at a dose of 25 µg.

In a 12-week, randomized, double-blind, placebo-controlled, parallel-group study aiming to assess efficacy and safety of once-daily umeclidinium at two different doses (62.5 µg and 125 µg) in patients with moderate-to-very severe COPD, umeclidinium at both doses significantly improved mean change from baseline in trough FEV₁ on day 84 (primary outcome) compared with placebo.³⁰ Improvements in dyspnea and health status were also observed with umeclidinium, without any increase in incidence of adverse events over placebo.³⁰

A pooled meta-analysis including phase III clinical trials and comparative studies in patients with moderate-to-very severe COPD shows that umeclidinium is superior to vilanterol and placebo in improving FEV₁ and reducing SGRQ score, and more effective than placebo in improving TDI and prolonging the time to first COPD exacerbation.³¹

Vilanterol, a LABA with inherent 24-h activity, was developed with fluticasone furoate, a once-daily ICS, in an FDC for asthma and COPD, and with a umeclidinium, a LAMA, in an FDC for COPD. In preclinical models, vilanterol showed a significantly faster onset of action than salmeterol and a longer duration of action than both salmeterol and formoterol,³² suggesting its potential for once-daily pharmacological treatment that may lead to increasing patients' compliance and adherence to therapy.

In a DPI FDC with umeclidinium at a dose of 62.5 µg, vilanterol at a dose of 25 µg is approved for once-daily maintenance treatment of COPD.³³ In a DPI FDC with fluticasone furoate 100 µg, vilanterol 25 µg is approved for once-daily maintenance treatment of COPD.³⁴ For once-daily treatment of persistent asthma, vilanterol 25 µg is approved in two strengths of fluticasone furoate (100 µg and 200 µg). Unlike other once-daily LABA, including indacaterol and olodaterol, vilanterol was not developed for monotherapy of COPD.^{33,34}

Using two separate DPIs, efficacy of triple therapy with vilanterol/fluticasone plus umeclidinium was

evaluated in two 12-week, double-blind, placebo-controlled, multicenter studies.³⁵ COPD patients were randomized 1:1:1 to receive once-daily blinded umeclidinium 62.5 µg, umeclidinium 125 µg or placebo added to open-label fluticasone/vilanterol (100/25 µg). In both studies, trough FEV₁ on day 85 (primary outcome measure) was significantly improved with fluticasone/vilanterol plus umeclidinium (62.5 µg and 125 µg) compared to fluticasone/vilanterol plus placebo.³⁵ In both studies, safety profiles, including cardiovascular adverse events and pneumonia, were similar across treatments.³⁵

Pharmacokinetics and pharmacodynamics parameters and safety of fluticasone furoate/vilanterol/umeclidinium FDC triple therapy *via* a single DPI compared with different FDC of dual therapies was investigated in healthy subjects in two phase I single-center, four-way, single-dose, crossover studies.³⁶ In particular, study CTT116415 [ClinicalTrials.gov identifier: NCT01691547] evaluated fluticasone furoate/vilanterol/umeclidinium at a single dose of 400/100/500 µg *versus* single doses of fluticasone furoate/vilanterol 400/100 µg, fluticasone furoate/umeclidinium at 400/500 µg or umeclidinium/vilanterol at 500/100 µg; study 200587 [ClinicalTrials.gov identifier: NCT01894386] compared single doses of 400/100/500 µg or 400/100/250 µg fluticasone furoate/vilanterol/umeclidinium with a single dose of umeclidinium/vilanterol 250/100 µg or fluticasone furoate/vilanterol 400/100 µg. A total of 88 healthy subjects were randomized to receive four consecutive inhalations (each administered as a single dose) *via* a single inhaler. Following single doses, similar total systemic exposure to fluticasone furoate, vilanterol and umeclidinium was observed when drugs were administered as triple FDC by a single DPI or as dual FDC therapy with fluticasone/vilanterol or umeclidinium/vilanterol. Adverse effect rate was low and similar across treatments.³⁶

The FULFIL trial was the first study evaluating single-inhaler triple therapy with fluticasone furoate/vilanterol/umeclidinium *versus* budesonide/formoterol dual therapy in GOLD Group D patients with COPD.³⁷ This randomized, double-blind, double-dummy trial included 1810 patients according to the intent-to treat population, and showed that change from baseline in trough FEV₁ and change from baseline in SGRQ total score at week 24 (co-primary endpoints) were significantly

improved after single-inhaler triple therapy compared with single-inhaler dual therapy. Regarding secondary outcome measures, the annualized rate of moderate to severe COPD exacerbations was significantly reduced after single-inhaler fluticasone furoate/vilanterol/umeclidinium FDC compared with budesonide/formoterol FDC [−35%; 95% confidence interval (CI), 14–51%; *p* = 0.002]. No between-group differences in adverse events were reported.³⁷ These data, showing efficacy and safety of fluticasone furoate/vilanterol/umeclidinium FDC in patients with very severe COPD, suggest that once-daily single-inhaler triple therapy might be a valid pharmacological strategy in these patients, also in view of the potential increase in adherence to therapy and reduction in inhaler device use errors (Table 1).³⁷

The IMPACT trial, a 52-week phase III, randomized, double-blind, three-arm, parallel-group, global multicenter study comparing the rate of moderate and severe exacerbations (primary outcome measure) between single-inhaler fluticasone furoate/umeclidinium/vilanterol and single-inhaler fluticasone furoate/vilanterol or umeclidinium/vilanterol in 10,357 patients with severe-to-very severe COPD was completed in July 2017 and publication of results is awaited [ClinicalTrials.gov identifier: NCT02164513].³⁸ Secondary outcome measures include changes from baseline in FEV₁ and SGRQ total score, and the annual rate of exacerbations in patients with peripheral blood eosinophilia.³⁸ The IMPACT trial is potentially pivotal in view of the large number of patients included, the choice of exacerbation rate as primary outcome measure, and the comparison of single-inhaler triple ICS/LABA/LAMA therapy with single-inhaler dual LAMA/LABA therapy. The last point is of particular relevance, as the lack of similar studies represents an unmet need in pharmacological treatment of COPD.³⁹

Regulatory aspects

On 18 September 2017, once-daily single DPI fluticasone furoate/umeclidinium/vilanterol trifenate FDC (100 µg/62.5 µg/25 µg predispensed dose corresponding to 92 µg/55 µg/22 µg delivered dose) (Trelegy Ellipta® GSK, Brentford, United Kingdom) was approved in the USA for the long-term, once-daily, maintenance treatment of patients with COPD, who are on an FDC of fluticasone furoate and vilanterol for airflow obstruction and

Table 1. Characteristics of studies evaluating triple inhaled therapy with fluticasone furoate, umeclidinium and vilanterol.

Study	Single inhaler	Randomization	Study type	Treatment arms	Number of subjects	Duration	Primary outcome	Secondary outcome and other parameters evaluated
Siler and colleagues study A ³⁵	No	Yes	Multicenter	<ul style="list-style-type: none"> • UMEC (62.5 µg) + FF/VI (100/25 µg) • UMEC (125 µg) + FF/VI (100/25 µg) • Placebo + FF/VI (100/25 µg) 	727 COPD patients	12 week	change from baseline in trough FEV ₁	0–6 h post-dose weighted mean FEV ₁ at day 84 SGRQ score Adverse events
Siler and colleagues study B ³⁵	No	Yes	Multicenter	<ul style="list-style-type: none"> • UMEC (62.5 µg) + FF/VI (100/25 µg) • UMEC (125 µg) + FF/VI (100/25 µg) • Placebo + FF/VI (100/25 µg) 	730 COPD patients	12 week	Change from baseline in trough FEV ₁	0–6 h post-dose weighted mean FEV ₁ at day 84 SGRQ score Adverse events
Brealey and colleagues study A ³⁶	Yes	Yes	Single center	<ul style="list-style-type: none"> • FF/UMEC/VI (400/500/100 µg) • FF/VI (400/100 µg) • FF/UMEC (400/500 µg) • UMEC/VI (500/100 µg) 	44 healthy subjects	48 h	PK/PD parameters	Adverse events, serious adverse events, laboratory values, vital sign, physical examination
Brealey and colleagues study B ³⁶	Yes	Yes	Single center	<ul style="list-style-type: none"> • FF/UMEC/VI (400/500/100 µg or 400/250/100 µg) • UMEC/VI (250/100 µg) • FF/VI (400/100 µg) 	44 healthy subjects	24 h	PK parameters	Adverse events, serious adverse events, laboratory values, vital sign, physical examination
Lipson and colleagues ³⁷	Yes	Yes	Multicenter	<ul style="list-style-type: none"> • FF/UMEC/VI • Budesonide/formeterol 	1810 COPD patients	24 weeks	Composite: Change from baseline in trough FEV ₁ Change from baseline in SGRQ total score	Efficacy and safety, including exacerbation rate, adverse events, pneumonia, cardiovascular events, bone fractures

COPD, chronic obstructive pulmonary disease; FEV₁, forced expiratory volume in 1 s; FF, fluticasone furoate; PD, pharmacodynamics; PK, pharmacokinetics; SGRQ, St. George's Respiratory Questionnaire; UMEC, umeclidinium; VI, vilanterol.

reducing exacerbations in whom additional treatment of airflow obstruction is required or for patients who are already receiving umeclidinium and an FDC of fluticasone furoate and vilanterol.⁴⁰

Following this approval by the US Food and Drug Administration (FDA), single DPI fluticasone furoate/umeclidinium/vilanterol trifenate FDC will soon be available in the USA. Regulatory applications have been submitted and are undergoing assessment in a number of other countries, including Australia and Canada.

The European Commission granted a marketing authorization valid throughout the European Union for twice-daily single pressurised metered dose inhaler (pMDI) beclomethasone dipropionate/formoterol fumarate/glycopyrronium FDC (100 µg/6 µg/10 µg) (metered dose corresponding to 87 µg/5 µg/9 µg delivered dose) (Trimbow[®], Chiesi Farmaceutici, Parma, Italy) on 17 July 2017⁴¹ and for once-daily single DPI fluticasone furoate/umeclidinium/vilanterol FDC (100 µg/62.5 µg/25 µg predispensed dose corresponding to 92 µg/55 µg/22 µg delivered dose) (Trelegy Ellipta[®]) on 15 November 2017.⁴²

These triple single-inhaler therapies are indicated as a maintenance treatment in adult patients with moderate to severe COPD who are not adequately treated by a combination of an ICS and a LABA.^{41,42}

Critical issues for inhaled triple therapy for COPD

At present, there is a discrepancy between GOLD recommendations on inhaled triple therapy and real-world prescription patterns in patients with COPD.^{14,15}

Current GOLD guidelines are cautious on triple therapy as they emphasize that more evidence is required to draw conclusions on benefits of triple LABA/LAMA/ICS FDC compared with available dual FDC, mainly dual LAMA/LABA.¹⁵

The TRILOGY²⁷ and FULFIL trials³⁷ have shown that single-inhaler ICS/LABA/LAMA FDC are more effective than single-inhaler dual ICS/LABA therapy in improving clinical outcome measures in patients with COPD, whereas the TRINITY trial²⁸ reported the superiority of single-inhaler triple therapy over tiotropium monotherapy. Healthcare resource utilization data and associated costs from the FULFIL trial show that, in a clinical trial

setting over a 24- or 52-week timeframe, non-drug costs for single-inhaler fluticasone furoate/umeclidinium/vilanterol triple therapy are lower than those for twice-daily budesonide/formoterol.⁴³ However, total annualized cost over 24 weeks for triple inhaled therapy was slightly greater than that for budesonide/formoterol.⁴³

The FLAME study showed that, compared with an ICS/LABA FDC, a LABA/LAMA FDC reduced COPD exacerbation rate (primary outcome measure) and improved both lung function and health-related quality of life with a significant lower rate of pneumonia in patients with COPD.⁴⁴ However, comparative prospective randomized clinical trials aiming to assess single-inhaler triple therapy containing an ICS *versus* dual LAMA/LABA therapy in COPD are currently not available. These studies are required to define the therapeutic role of single-inhaler triple FDC in COPD management.³⁹ While the central role of bronchodilators in COPD is clearly established, the response to ICS seems to be highly variable in the general population of COPD patients.⁴⁵ Moreover, phenotypes of COPD patients including frequent exacerbators and ACOS are most likely to respond to these drugs.¹⁷ In this context, selecting the 'right' target population(s) seems to be pivotal when planning studies aiming to compare triple ICS/LABA/LAMA therapy *versus* dual LABA/LAMA therapy.

Despite guidelines recommendations,^{15,46} triple inhaled therapy is widely prescribed in patients with COPD.¹⁴ Analysis of prescribing pathways in COPD patients without asthma attending 387 primary-care practices across the United Kingdom from 2002 to 2010 shows that, during the study period, 32% of patients received triple therapy.¹⁴ After a diagnosis of COPD, patients in GOLD Group A, B, C and D progressed to triple inhaled therapy in 19%, 28%, 37% and 46% of cases, respectively.¹⁴ A major factor involved in progression to triple inhaled therapy seems to be the number of exacerbations.¹⁴

These data show a trend toward triple inhaled therapy prescriptions as COPD severity increases. In this study, about 50% of patients with most severe COPD ended up having a prescription for ICS/LABA/LAMA, despite the lack of prospective randomized clinical trials showing the superiority of this therapeutic option over dual bronchodilator FDC. Even more interestingly, 19% of Group A COPD patients who would require a single bronchodilator according to

GOLD recommendations ended up having triple inhaled therapy.

Inappropriate adoption of triple inhaled therapy exposes patients to avoidable side effects. In particular, LABA can produce resting sinus tachycardia and precipitate cardiac rhythm disturbances in susceptible patients. Also, metabolic side effects could occur, especially in patients with chronic heart failure⁴⁷ or being treated with thiazide diuretics;⁴⁸ less frequent are muscle tremors, nervousness and occasional insomnia. Under treatment with LAMA, polar quaternary ammonium compounds with low lipid solubility, incidence of systemic side effects is generally low because of poor absorption, which limits systemic exposure. One of the most common side effects is dry mouth.⁴⁹ In a nested case-control study including 284,220 LABA-LAMA-naïve patients with COPD, initiation of treatment with LAMA or LABA was associated with about 1.5-fold increase in cardiovascular risk, irrespective of history of cardiovascular disease or COPD exacerbations.⁵⁰ LAMA dosage forms, individual LABAs and concomitant COPD therapeutic regimens did not differ in the cardiovascular risks.⁵⁰

A systematic review and meta-analysis of 42 randomized trials including about 50,000 patients with COPD raised concerns about tiotropium soft mist inhaler as increased risk of overall mortality compared with other medications, including LABA/ICS and tiotropium DPI, was reported.⁵¹ The TIOSPIR study, a randomized, double-blind, parallel-group trial involving 17,135 patients with COPD which was specifically designed to address this safety issue showed that tiotropium soft mist inhaler at a dose of 5 µg once daily was noninferior to tiotropium DPI at a dose of 18 µg once daily with respect to the risk of death (hazard ratio, 0.96; 95% CI, 0.84 to 1.09).⁵²

Adverse events associated with the use of ICS include increased risk of any pneumonia and pneumonia requiring hospitalization.⁵³ A pooled analysis of trials comparing ICS/LABA *versus* placebo shows that treatment with dual active component inhalers is associated with higher risk of pneumonia.⁵⁴ Other potential side effects of ICS include increased risk of cataracts,⁵⁵ pulmonary tuberculosis,⁵⁶ diabetes onset and diabetes progression,⁵⁷ and nonvertebral fractures.⁵⁸

However, safety issues are not the only concern related to use/overuse of ICS as lack of efficacy

of these drugs in the general COPD population was reported. A retrospective general practice cohort study in the United Kingdom has shown that the rate of exacerbations requiring hospitalizations did not change, notwithstanding the increased number of prescriptions for LABA plus ICS combinations.⁵⁹

In a 52-week, double-blind, parallel-group study including 2485 patients with a history of COPD exacerbation who received tiotropium DPI (at a dose of 18 µg once daily), salmeterol DPI (50 µg twice daily) and the fluticasone propionate DPI (500 µg twice daily) during a 6-week run-in period and were then randomized to continued triple therapy or withdrawal of fluticasone propionate in three steps over a 12-week period, the time to the first moderate or severe COPD exacerbation (primary outcome measure) was similar in the two study groups (hazard ratio, 1.06; 95% CI, 0.94 to 1.19), whereas the adjusted mean reduction from baseline in the trough FEV₁ was 38 ml greater in the glucocorticoid-withdrawal group than in the glucocorticoid-continuation group.⁶⁰

Unlike the general COPD population, subphenotypes of COPD patients might have a better response to ICS.

A post-hoc analysis of data from two 52-week, parallel, randomized, controlled trials, aiming to compare three doses of fluticasone furoate (50 µg, 100 µg and 200 µg) added to vilanterol 25 µg with vilanterol alone 25 µg in 3177 patients with moderate to severe COPD with at least one exacerbation in the previous year, showed that, across all ICS doses, reduction in COPD exacerbation rates was significant in those patients with peripheral blood eosinophil cell counts $\geq 2\%$ (-29% , $p < 0.0001$), but not in patients with peripheral blood eosinophil cell counts $< 2\%$ (-10% , $p = 0.28$).¹² Of note, in COPD patients with the eosinophilic phenotype, the extent of reduction in exacerbation rate was correlated with baseline peripheral blood eosinophil cell counts.¹² These findings suggest that blood eosinophilia might predict response to ICS in patients with COPD.¹² However, large controlled prospective studies are required to formally address this issue.

Conclusion and future perspectives

At present, the choice of triple inhaled therapy seems to rely mostly on an empirical basis rather than on a rational subphenotyping approach.¹⁷

ICA/LABA/LAMA overprescription patterns likely reflect the attitude of physicians to provide COPD patients with the 'maximal' level of pharmacological treatment in the attempt to slow down the rapid decline in lung function that characterizes this disease. However, in the lack of a demonstrated response to ICS in the individual subject, large-scale prescription of FDC containing an ICS should be avoided due to poor long-term tolerability of these drugs, particularly at the high doses indicated for COPD. As pointed out by GOLD and other guidelines, triple inhaled therapy should be limited to patients with more severe COPD who are not adequately controlled with dual LABA/LAMA therapy. In these patients, single-inhaler triple therapy, including fluticasone furoate/vilanterol/umeclidinium FDC, seems to be an attractive and convenient pharmacological strategy for maintenance COPD treatment. Attempts should be made to identify patients with COPD phenotypes most likely to respond to the ICS component of triple inhaled therapy (e.g. eosinophilic, ACOS and frequent exacerbators). Single-inhaler triple therapy with fluticasone furoate, umeclidinium and vilanterol, which is in phase III development, seems to be an effective and well-tolerated therapeutic option in patients with COPD. The FULFIL trial has shown the superiority of this triple inhaled FDC over inhaled budesonide/formoterol, but comparative studies with LABA/LAMA are currently lacking.

The key question is whether fluticasone furoate/vilanterol/umeclidinium is superior to vilanterol/umeclidinium in patients with severe-to-very severe COPD and if there are differences in drug response based on phenotypes. Results from the IMPACT study, a large phase III study aiming at comparing efficacy and safety of triple fluticasone furoate/vilanterol/umeclidinium with either vilanterol/umeclidinium or fluticasone furoate/vilanterol in different COPD phenotypes/endotypes, will likely fill the gap and answer this question.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

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