SYSTEMATIC REVIEW REPORT:

TRELEGY ELLIPTA single inhaler triple therapy for treatment of adult patients with moderate-to-severe chronic obstructive pulmonary disease (COPD)

Therapeutics Initiative report

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A systematic review of TRELEGY ELLIPTA single inhaler triple therapy for treatment of adult patients with moderate-to-severe chronic obstructive pulmonary disease (COPD)

Executive Summary

1. Background

Chronic obstructive pulmonary disease (COPD) is a progressive disease characterized by airway inflammation and airflow limitation that is not fully reversible. The goal of COPD treatment is to prevent acute moderate to severe exacerbations, improve quality of life and reduce symptoms such as dyspnea. The main treatment options belong to a number of pharmacological classes: bronchodilators (short-acting $beta_2$ agonists [SABA], long-acting $beta_2$ agonists [LABA], short-acting muscarinic antagonists [SAMA], and long-acting muscarinic antagonists [LAMA]), inhaled corticosteroids [ICS], and inhibitors of the enzyme phosphodiesterase-4 [PDE4 inhibitors]. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) report recommends stepwise intensification to triple therapy in those patients (classified as "group D") with persisting symptoms and who still have frequent exacerbations despite maximal dual therapy with either LAMA/LABA or LABA/ICS drug therapy. Trelegy Ellipta is a new triple fixed-dose combination of umeclidinium 62.5 mcg (LAMA), fluticasone furoate 100 mcg (ICS), and vilanterol 25 mcg (LABA) that is indicated for the long-term, once daily, maintenance treatment of COPD, including chronic bronchitis and/or emphysema in patients who are not adequately treated by a combination of an ICS/LABA. It is not indicated to treat acute bronchospasm or asthma. This is the only triple therapy inhaler licensed in Canada.

2. Requested Research Question

In double blind active controlled parallel group RCTs of at least 24 weeks duration, does triple therapy with fluticasone furoate 100mcg/umeclidinium 62.5 mcg/vilanterol 25 mcg (FF/UMEC/VI) prevent acute moderate to severe exacerbations, improve quality of life and reduce dyspnea symptoms as compared to combination therapy with 2 drugs (UMEC 62.5 mcg/VI 25 mcg or FF 100 mcg/VI 25 mcg or UMEC 62.5 mcg/FF 100 mcg), all administered once daily as a single inhaler or multiple inhalers, in adult patients with symptomatic COPD (diagnosed FEV1/FVC <0.70) who are not adequately treated by a combination of an ICS/LABA (i.e. classified as Group D in the GOLD report)?

3. Methods

Ovid MEDLINE, MEDLINE In-Process, MEDLINE Ahead of Print, Ovid Embase, the Cochrane Central Register of Controlled Trials (CENTRAL), and EBSCO CINAHL were searched from dates of inception until June 2018. We also searched clinicaltrials.gov, Drugs@FDA, European Medicines Agency public assessment reports and the manufacturer's website for all relevant RCT reports. Reports prepared by independent groups such as FDA, Health Canada, European Medicines Agency (EMA), Prescrire, NICE, AHRQ and Drug Therapy

Bulletin (DTB) were retrieved and summarized. Outcomes were analyzed in order of clinical importance (i.e. a health outcome hierarchy) recognizing that not all outcomes are of equivalent value and not all evidence has uniform protection against bias. Meta-analysis was carried out whenever possible. Risk of bias was assessed according to the Cochrane risk of bias tool and helped to inform conclusions.

4. Summary of Available Evidence

Only IMPACT 2018, a double blind RCT in 10,355 patients with symptomatic COPD and a history of exacerbation within a year before enrolment met the inclusion criteria for this review. This 1-year study compared triple therapy with FF/UMEC/VI (n=4151) with UMEC/VI (n=4134) and FF/VI (n=2070), all administered once daily as a single inhaler, in patients who were classified as Group D, using the GOLD criteria. The same drugs and doses of ICS, LABA and LAMA were used in the triple-therapy and comparator groups. No studies were identified that compared FF/UMEC/VI with FF/UMEC.

The mean age of study participants was 65.3 (± 8.3) years, 66% male, and 65% former smokers. Post-bronchodilator FEV_1 was 45.5% of predicted normal value and a mean CAT score of 20.1 (± 6.1) at screening. Fourty-seven percent and 26% had a history of ≥2 moderate COPD exacerbations and ≥1 severe COPD exacerbation, respectively. Patients with a history of asthma were included in the study. Nearly 40% of the patients were receiving triple therapy, and more than 70% were receiving ICS at baseline.

9087 patients (88%) completed the trial and 7991 (77%) completed the trial while receiving randomized therapy. This study used intention to treat to analyze safety and efficacy. Patients who permanently discontinued study treatment did not receive further evaluation but were encouraged to continue in the study by participating in telephone contacts in order to assess exacerbations, SAEs and concomitant medications post-treatment. The proportion of patients successfully contacted was not reported. The accuracy and completeness of phone call information was not reported. Vital status was available for 9781 (94.4%) of the total study population at Week 52.

Given that nearly 40% of the patients were receiving triple therapy and more than 70% were receiving a COPD regimen that included ICS at randomization, a major confounder in IMPACT 2018 is “stepping down” of therapy in patients randomized to either dual therapy group. In particular, ICS was abruptly withdrawn at randomization in those patients assigned to the dual bronchodilator (UMEC/VI) group, which included patients with a history of asthma. Evidence from at least 2 double blind, placebo controlled, parallel group RCTs in moderate to severe COPD patients with a history of exacerbations report that abrupt withdrawal of ICS increased the risk of moderate or severe exacerbations [RR 1.6 (95% CI 1.2,2.2); HR 1.5 (95% CI 1.1,2.1)].

IMPACT 2018 was judged to have a high risk of bias according to the Cochrane Risk of Bias Tool with respect to attrition, selective reporting and source of funding. There are also

other biases with respect to study design and presence of confounding that misrepresent the treatment effect.

5. Results and Interpretation

IMPACT 2018 randomized patients with symptomatic COPD and a history of exacerbations despite being on triple therapy (38%) and combination therapy with ICS/LABA (29%) or LAMA/LABA (9%) at baseline.

The published study reports on total mortality during treatment, whereas the Supplementary Appendix provides data on all-cause mortality that occurred on- and off-treatment for 94.4% of randomized patients. Time-to-first-event analysis found that the reduction in total mortality with triple therapy was statistically significant [HR 0.71(95% CI 0.51,0.99); p=0.043] as compared to UMEC/VI. There was no difference in the time-to-event analysis of mortality between triple therapy and FF/VI group. Our independent analysis of mortality events (not time-to-event) during the 1-year study found the differences in total mortality between triple therapy with FF/UMEC/VI were not statistically significant: FF/UMEC/VI versus FF/VI = 89 (2.1%) vs 97 (2.4%) RR 0.91 (0.69,1.21) and FF/UMEC/VI versus UMEC/VI = 89 (2.1%) vs 60 (2.9%) RR 0.74 (0.54,1.02) The discrepancy between the time-to-event analysis performed by the study authors and our analysis cannot be explained by available data.

Total SAEs (which includes all cause hospitalization and hospitalization due to severe exacerbation), total adverse events and withdrawal due to adverse events were not reduced with triple therapy as compared to either dual therapy combination. The risk of clinician-diagnosed pneumonia was significantly higher with triple therapy than with UMEC/VI but not with FF/VI. However, this event rate is not reported on the total patient population.

The study reports a reduction in the annual rate of moderate or severe exacerbations with triple therapy [rate ratio 0.75 (95% CI 0.70,0.81); 25% difference; P<0.001 versus UMEC/VI; rate ratio 0.85 (95% CI 0.80,0.90); 15% difference; P<0.001 versus FF/VI]. However, these rates do not include full reporting of about 25% of the study sample (18, 25 and 27% in UMEC/FF/VI, FF/VI and UMEC/VI, respectively). Also, the number of patients with one or more moderate or severe exacerbation was not reported. Instead, the paper reports the average number of exacerbations in a group. Patients with 2-3 exacerbations in a year are very different than people with 0 to 1 in the study period, but their differences are hidden in a 'average' annual rate. The number of patients with one or more exacerbations could, in fact, be similar in the two groups, which changes the clinical relevance of this finding.

The annual rate of severe exacerbations was significantly lower with UMEC/FF/VI as compared to UMEC/VI [rate ratio 0.66 (95% CI 0.56,0.78); P<0.001] but was not significantly lower compared with FF/VI. The number of patients hospitalized due to severe exacerbation is not reported. Only presenting the average number of severe exacerbations is similar to only reporting total exacerbations, noted above.

Total SAEs, which includes hospitalizations for reasons other than exacerbations of COPD were not significantly reduced with triple therapy. Total SAEs provides the best summary statistic of therapeutic impact accounting for all known and unknown serious impact (benefit and harm) from therapy.

Time-to-first-event analysis found that triple therapy was associated with a lower risk of moderate or severe exacerbations during treatment than either dual therapy [HR 0.85 (95% CI 0.80 to 0.91; 15% difference; P<0.001 versus FF/VI; HR 0.84 (95% CI 0.78 to 0.91; 16% difference; P<0.001 versus UMEC/VI]. However, time-to-first-event analysis cannot be interpreted correctly without knowing how many patients had more than one exacerbation during the study period. In addition, time-to-first-event analysis is biased by an increase in exacerbations following abrupt withdrawal of ICS and LAMA in the UMEC/VI group and FF/VI groups, respectively.

Quality of life (SGRQ) and dyspnea symptoms (TDI) were evaluated in 49 and 76% of randomized patients, respectively. Triple therapy improved SGRQ and TDI scores, in these subgroups, but the results are not considered valid due to missing data.

Use of rescue salbutamol, a protocol-defined endpoint, was not reported in the published study. This is a key outcome measure that needs to be reported to corroborate any claim regarding symptomatic improvement in patients.

COPD related health care utilization, which includes physician visits/ER visits and hospitalizations, is another protocol-defined endpoint that was not reported in the published material. These findings would corroborate the findings of decreased rate of acute moderate to severe exacerbation.

In a subset of 7916 (76%) patients evaluated, triple therapy improved trough FEV_1 more than dual therapy comparators. The finding of improved FEV_1 with triple therapy is unreliable, because of the FEV1 values are un-reliable and because data for 24% of randomized patients are missing.

6. Conclusion

There is insufficient evidence that triple therapy with FF/UMEC/VI provides therapeutic advantage versus dual therapy (FF/VI or UMEC/VI) in terms mortality, total serious adverse events (which includes all cause hospitalization and hospitalization due to severe exacerbation), moderate exacerbations, total adverse events or withdrawal due to adverse events, COPD symptoms or quality of life.

A systematic review of TRELEGY ELLIPTA single inhaler triple therapy for treatment of adult patients with moderate-to-severe chronic obstructive pulmonary disease (COPD)

Background

Diagnosis and management of COPD

Chronic obstructive pulmonary disease (COPD) is a progressive disease characterized by airway inflammation and airflow limitation that is not fully reversible. It occurs as a consequence of exposure to noxious particles or gases. Exposure to cigarette smoke is the most common risk factor. Drugs to treat COPD are licensed by regulatory authorities based on short-term randomized trials (typically 12 weeks in duration) that show an improvement in the surrogate marker FEV_1 which is the primary outcome measure in most trials. However, the goal of treating COPD is to prevent acute moderate to severe exacerbations, improve quality of life and reduce symptoms such as dyspnea. (1)

The main treatment options for COPD belong to a number of pharmacological classes – bronchodilators (short-acting $beta_2$ agonists [SABA], long-acting $beta_2$ agonists [LABA], short-acting muscarinic antagonists [SAMA], and long-acting muscarinic antagonists [LAMA]), inhaled corticosteroids [ICS], and inhibitors of the enzyme phosphodiesterase-4 [PDE4 inhibitors]. Numerous clinical practice guidelines recommendations involve a stepwise intensification of drug therapy.

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) report has provided therapeutic recommendations for patients with COPD based on “ABCD” groups derived exclusively from patient symptoms and their assessment of exacerbation: (2)

1. **Group A** has modified MRC dyspnea scale (mMRC) 0-1, CAT <10 and 0 or 1 exacerbation not leading to hospital admission.
2. **Group B** has mMRC score ≥2, CAT ≥10 and 0 or 1 exacerbation not leading to hospital admission.
3. **Group C** has mMRC 0-1, CAT <10 and ≥2 exacerbation or ≥1 exacerbation leading to hospital admission.
4. **Group D** has mMRC score ≥2, CAT ≥10 and ≥2 exacerbation or ≥1 exacerbation leading to hospital admission.

The GOLD report provides a pharmacological treatment algorithm based on which group the patient belongs: (2,3)

Group A: Start with a short or long acting bronchodilator; evaluate effect; then continue, stop or try alternate class of bronchodilator. This should be continued if symptomatic benefit is documented.

Group B: Start with a long acting bronchodilator (LABA or LAMA). Long acting bronchodilators are superior to short acting bronchodilators taken as needed. There is no evidence to recommend one class of long acting bronchodilator over another for initial relief of symptoms in this group of patients. In the individual patient, the choice should depend on patient's perception of symptom relief. For patients with persistent breathlessness on monotherapy the use of 2 bronchodilators is recommended (LAMA/LABA). For patients with severe breathlessness initial therapy with 2 bronchodilators may be considered. If addition of the second bronchodilator does not improve symptoms treatment should be stepped down to a single bronchodilator.

Group C: Start with a single long acting bronchodilator. LAMA was superior to LABA regarding exacerbation prevention so start with LAMA in this group. Patients with persistent exacerbation may benefit from adding a second long acting bronchodilator (LAMA/LABA) or (LABA/ICS). An ICS increases risk of developing pneumonia in some patients so primary choice is LAMA/LABA.

Group D: Start with a LAMA/LABA combination, as it is superior to monotherapy with each class of drug. If single bronchodilator is chosen then LAMA is preferred for exacerbation prevention as compared to LABA.
LAMA/LABA combination was superior to LABA/ICS in preventing exacerbation and other patient reported outcomes. Also Group D patients are at higher risk of developing pneumonia when receiving treatment with ICS.
In some patients LABA/ICS may be first choice (history and/or findings of asthma-COPD; or in patients with high eosinophil counts).
In patients who develop further exacerbations on LAMA/LABA therapy then either switch to LABA/ICS or add ICS to LAMA/LABA.
If patients on triple therapy still have exacerbations then:

a. Add roflumilast in patients with FEV_1 <50% predicted value and chronic bronchitis particularly if they experienced at least one hospitalization for an exacerbation in the previous year.
b. Add macrolide (azithromycin)
c. Stop ICS.

Triple therapies in a single inhaler for COPD

There are several triple therapies available in a single inhaler for COPD:

1. The Euopean Medicines Agency (EMA) has granted marketing authorisation for a pressurised metered dose inhaler (pMDI) Trimbow containing beclometasone dipropionate, formoterol fumarate dihydrate and glycopyrronium bromide (Trimbow – Chiesi Pharmaceuticals) for the treatment of COPD in patients not adequately treated with a combination of an inhaled corticosteroid (ICS) and a long-acting $beta_2$ agonist (LABA). **This combination is not available in Canada.**

2. A new triple fixed-dose combination of tiotropium 18 mcg, salmeterol 50 mcg and fluticasone 500 mcg was evaluated in Aaron et al study. (5) **This combination is not available in Canada.**

3. A new triple therapy inhaler **TRELEGY ELLIPTA** (FF/UMEC/VI) containing fluticasone furoate 100 mcg, umeclidinium 62.5 mcg and vilanterol 25 mcg is a combination of ICS, LAMA and LABA, and is indicated for the long-term, once daily, maintenance treatment of COPD, including chronic bronchitis and/or emphysema in patients who are not adequately treated by a combination of an ICS/LABA. It is not indicated to treat acute bronchospasm or asthma. (6) This is the only triple therapy inhaler licensed in Canada.

It is important to note that each component in FF/UMEC/VI is approved as a single entity or as a component in a dual combination product for treatment of COPD.

GlaxoSmithKline has submitted adequate in-vitro and PK data to the US Food and Drug Administration (FDA) demonstrating a lack of pharmaceutical differences between FF/VI + UMEC and FF/UMEC/VI. These data demonstrate that the delivery of FF, UMEC and VI delivery is comparable whether administered as UMEC + FF/VI via two separate inhalers or from a single inhaler containing FF/UMEC/VI. (7)

TRELEGY ELLIPTA indication

TRELEGY ELLIPTA is indicated for the long-term, once daily, maintenance treatment of chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema in patients who are not adequately treated by a combination of an ICS/LABA.

It is NOT indicated for the relief of acute bronchospasm.

It is NOT indicated for the treatment of asthma.

Mechanism of action of each component of TRELEGY ELLIPTA

Umeclidinium 62.5 mcg is available as dry powder for oral inhalation and is indicated once daily for the long-term once-daily maintenance bronchodilator treatment of airflow obstruction in patients with COPD, including chronic bronchitis and emphysema. It is **not** indicated for the relief of acute deterioration of COPD. It is a long-acting muscarinic receptor antagonist (LAMA), also referred to as a long-acting anticholinergic. It is a quinuclidine derivative that is a muscarinic receptor antagonist with activity across multiple muscarinic cholinergic receptor subtypes. Following oral inhalation, it acts locally on airways to produce bronchodilation. Umeclidinium exerts its 24-hour bronchodilatory activity by competitively inhibiting the binding of acetylcholine with muscarinic acetylcholine receptors on airway smooth muscle. (8)

Vilanterol 25 mcg monotherapy is **NOT** available as single inhaler. It is available in combination with fluticasone furoate. (Breo® Ellipta). It is indicated for the long-term once-daily maintenance treatment of airflow obstruction in patients with COPD, including chronic bronchitis and/or emphysema, and to reduce exacerbations of COPD in patients with a history of exacerbations. The recommended dose is 100/25mcg once daily or 200/25mcg once daily. (9) Vilanterol is a selective LABA, with bronchodilatory effects maintained for 24-hours. The pharmacologic effects of beta2-adrenoceptor agonist drugs, including vilanterol, are at least in part attributable to stimulation of intracellular adenyl cyclase, the enzyme that catalyzes the conversion of adenosine triphosphate (ATP) to cyclic-3',5'-adenosine monophosphate (cyclic AMP). Increased cyclic AMP levels cause relaxation of bronchial smooth muscle and inhibit the release of mediators of immediate hypersensitivity from cells, especially mast cells. (9)

Fluticasone furoate 100mcg is a synthetic trifluorinated corticosteroid with potent anti-inflammatory activity. The precise mechanism through which fluticasone furoate affects COPD symptoms is not known. Inflammation is an important component in the pathogenesis of COPD. Corticosteroids have been shown to have a wide range of actions on multiple cell types (e.g., mast cells, eosinophils, neutrophils, basophils, macrophages, lymphocytes) and mediators (e.g., histamine, eicosanoids, leukotrienes, cytokines) involved in inflammation. (9)

There is evidence from randomized controlled studies that ICS use is associated with higher prevalence of oral candidiasis, hoarse voice, skin bruising and pneumonia. (10). Regular treatment with ICS increases risk of pneumonia especially in those with severe disease. (2,11)

Requested research question

The policy relevant research question was operationalized for systematic review design using a PICOS approach to research question formulation. Studies were selected for inclusion in the systematic review based on the predetermined selection criteria presented below:

Participants: Adult patients with symptomatic COPD (diagnosed $FEV_1/FVC < 0.70$) who are not adequately treated by a combination of an ICS/LABA.

According to GOLD guidelines, ONLY GOLD group D has an indication for triple therapy (mMRC score ≥2, CAT ≥10 and ≥2 exacerbation or ≥1 exacerbation leading to hospital admission).

Intervention: Triple therapy with fluticasone furoate 100mcg/umeclidinium 62.5 mcg/vilanterol 25 mcg (FF/UMEC/VI) once daily administered as a single inhaler or multiple inhalers.

Comparators: Combination therapy with 2 drugs (UMEC 62.5 mcg/VI 25 mcg or FF 100 mcg/VI 25 mcg or UMEC 62.5 mcg/FF 100 mcg) once daily administered as a single inhaler or multiple inhalers.

Outcome hierarchy:

1. Total mortality
2. Total serious adverse events (including total hospitalizations)
3. Number of patients with one or more acute moderate or severe exacerbation
4. Quality of life measured by Saint George Respiratory Questionnaire (SGRQ) total score (≥ 4 point change in total score is considered as minimal clinically important difference in clinical trials; and a mean change in total score from baseline)
5. Time to first moderate or severe exacerbation
6. Improvement in symptoms such as dyspnea measured by Transition Dyspnea Index (TDI) score (≥ 1 point improvement is considered MCID in clinical trials; a mean change in TDI score)
7. Decreased need for rescue medications (an additional measure of symptom improvement)
8. Total adverse events
9. Total withdrawals
10. Withdrawal due to adverse events
11. COPD related health care utilization (physician visits/ER visits and hospitalization)
12. End of study trough FEV_1 (We accept there is an increase in FEV_1 – a surrogate outcome measure. We will provide range of improvement in FEV_1. Meta-analysis of this outcome will not be performed.)

Study design: Double blind randomized active controlled parallel group clinical trial of at least 24 weeks duration. Randomized active controlled clinical trials comparing triple therapy versus 2 drug combinations (LABA + LAMA) or (LABA + ICS) or (LAMA + ICS) NOT available in Canada are out of scope. Other study designs are also out of scope.

Methods

Search strategy

We searched Ovid MEDLINE, MEDLINE In-Process, MEDLINE Ahead of Print, Ovid Embase, the Cochrane Central Register of Controlled Trials (CENTRAL), and EBSCO CINAHL from dates of inception until June 2018. We also searched clinicaltrials.gov, Drugs@FDA, European Medicines Agency public assessment reports and the manufacturer's website for all relevant RCT reports. Reports prepared by independent groups such as FDA, Health Canada, EMA, Prescrire, NICE, AHRQ and Drug Therapy Bulletin (DTB), if available, were retrieved and summarized.

Study selection

The initial search of all the databases was performed to identify citations of potential relevance. The initial screen of these abstracts excluded articles whose titles and/or abstracts are clearly

irrelevant. The full texts of remaining articles were then retrieved (and translated into English where required). Two independent reviewers assessed the eligibility of the trials using a standardized trial selection form. A third reviewer resolved any discrepancies.

Data collection and analysis

Data abstraction was done by two independent reviewers. Review Manager 5.3 software of the Cochrane Collaboration was used to meta-analyze data. Results are presented as relative risks (RR) with 95% confidence intervals for dichotomous outcomes and as weighted mean difference (WMD) with 95% confidence interval for continuous outcomes.

Assessment of risk of bias in included studies

Risk of bias for each included trial was assessed using the Cochrane risk of bias tool which includes seven domains: Randomization; allocation concealment; blinding of participant and physician; blinding of outcome assessor; attrition bias; selective reporting bias; and other bias (e.g. conflict of interest bias - funding of study by the manufacturer or employee of the manufacturer is author of the study). Each domain was assessed as “Low”, “Unclear” or “High” risk of bias.

Evaluative framework

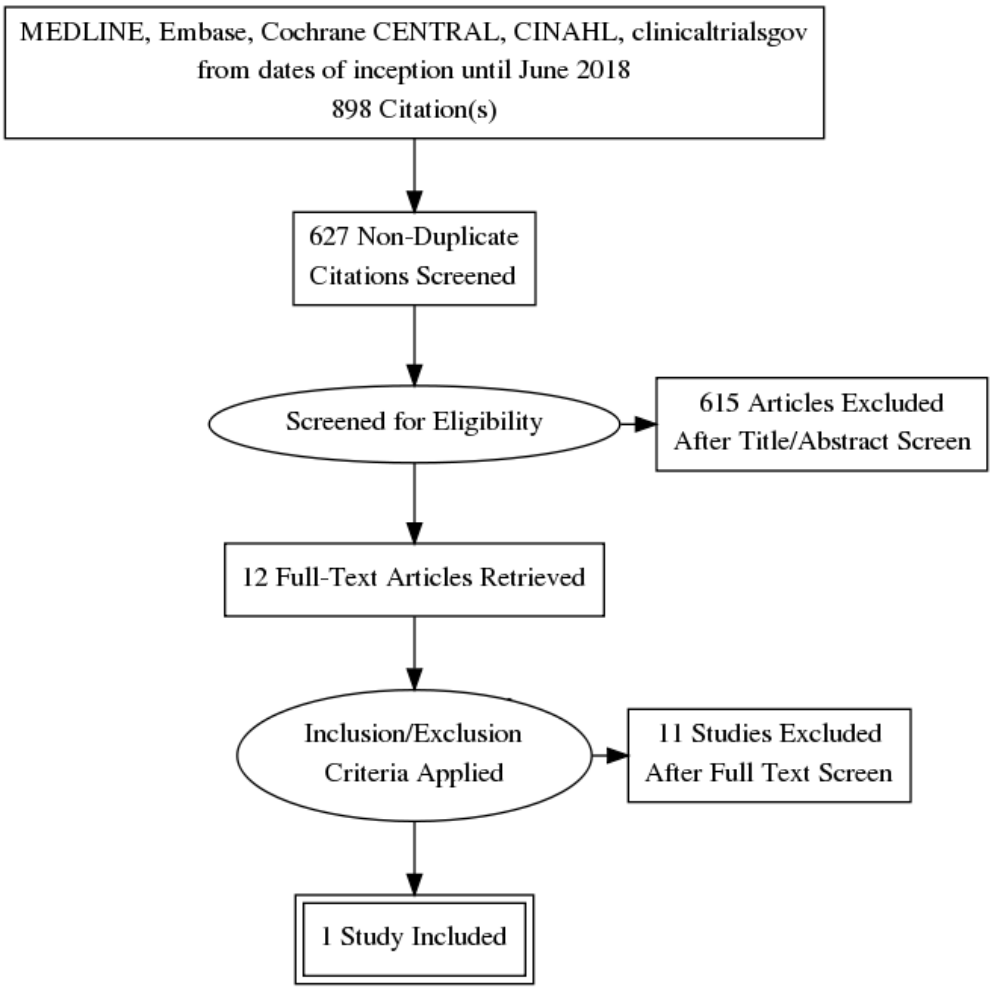
Evidence from various sources is organized and situated within a health outcome and evidence hierarchy. The principle is that health outcomes higher on the hierarchy are more important than those lower on the hierarchy. Recognizing that not all outcomes are of equivalent value and not all evidence has uniform protection against bias, the overall framework for the review was based on a hierarchy of outcomes provided in section 2. As much as possible, the hierarchy was completed for each included study.

Results

Findings from the literature

The sorting and inclusion process is documented using the PRISMA flowchart approach that is a standard systematic review method (Figure 1).

Figure 1: PRISMA flow diagram of study selection



Summary of excluded studies

Reasons for exclusion of the excluded studies are provided in Table 1.

Table 1: Excluded studies

Clinical Study ID/Reference	Reason for Exclusion
NCT01957163/GSK Study 200109/Siler 2016 (12)	Only 12 weeks duration. Specified triple therapy [(FF/VI 100/25 mcg) + UMEC 62.5 mcg] was administered via 2 inhalers and not as a single inhaler. The study also included triple therapy treatment arm with a higher dose of umeclidinium [(FF/VI 100/25 mcg) + UMEC 125 mcg]. The comparator was a 2 drug combination therapy FF/VI 100/25 mcg. Change from baseline in FEV_1 was the primary end point. Exacerbation outcome was not reported.

Clinical Study ID/Reference	Reason for Exclusion
NCT02119286/GSK Study 200110/Siler 2016 (12)	Only 12 weeks duration. Specified triple therapy [(FF/VI 100/25 mcg) + UMEC 62.5 mcg] was administered via 2 inhalers and not as a single inhaler. The study also included triple therapy treatment arm with a higher dose of umeclidinium [(FF/VI 100/25 mcg) + UMEC 125 mcg]. The comparator was a 2 drug combination therapy FF/VI 100/25 mcg. Change from baseline in FEV_1 was the primary end point. Exacerbation outcome was not reported.
NCT01772134/GSK Study AC4116135/Siler 2016 (12)	Randomized treatment with UMEC 62.5 mcg or UMEC 125 mcg added to open-label fluticasone propionate 250 mcg/salmeterol 50 mcg BID. LABA used is salmeterol instead of vilanterol for triple therapy.
NCT01772147/GSK Study AC4116136/Siler 2016 (12)	Randomized treatment with UMEC 62.5 mcg or UMEC 125 mcg added to open-label fluticasone propionate 250 mcg/salmeterol 50 mcg BID. LABA used is salmeterol instead of vilanterol for triple therapy.
NCT02345161/ GSK Study CTT116853/ FULFIL 2017 (13)	FF 100 mcg/UMEC 62.5 mcg/VI 25 mcg versus budesonide 400 mcg/formoterol 12 mcg used as comparator
NCT03478683 (14)	Ongoing DBRCT; budesonide 320 mcg/formoterol 9 mcg plus tiotropium 18 mcg used as comparator
NCT03474081 (15)	Ongoing DBRCT; tiotropium 18 mcg used as comparator
NCT03265145 (16)	Ongoing open label study; triple therapy not defined
NCT03467425 (17)	Ongoing open-label study; any non-ELLIPTA multiple Inhaler triple therapies in the usual care setting used as comparator
NCT03478696 (18)	Completed study but withdrawn; budesonide/formoterol plus tiotropium used as comparator; only 12 weeks duration
NCT02729051/Bremner 2018 (19)	A 24-week RCT comparing closed therapy with FF 100 mcg/ UMEC 62.5 mcg/VI 25 mcg in a single inhaler plus placebo in a separate inhaler versus FF 100 mcg/VI 25 mcg plus UMEC 62.5 mcg in a separate inhaler as open triple therapy. Two drug combination comparators were not included.

Description of included studies

Only IMPACT 2018, a double blind RCT in 10,355 patients with symptomatic COPD and a history of exacerbation within a year before enrolment, met the inclusion criteria for this review. (20) This study compared triple therapy with FF/UMEC/VI (n=4151) with UMEC/VI (n=4134) and FF/VI (n=2070), all administered once daily as a single inhaler, in patients who are classified as Group D in the GOLD report. The same agents and doses of ICS, LABA and LAMA were used in the triple-therapy and comparator groups. *No studies were identified that compared FF/UMEC/VI with FF/UMEC.* A description of the study characteristics is provided in Table 2.

Table 2: IMPACT 2018 study characteristics

Participants	N=10,355 symptomatic COPD (CAT score ≥ 10) patients ≥ 40 years of age with: 1) FEV_1 < 50% of predicted normal value and a history of ≥ 1 moderate or severe exacerbation in previous year; or 2) FEV_1 of 50-80% of predicted normal value and a history of ≥ 2 moderate or 1 severe exacerbation in previous year
Intervention	FF/UMEC/VI (100/62.5/25 mcg) OD administered as single inhaler (n=4151)
Comparators	FF/VI (100/25 mcg) OD administered as single inhaler (n=4134) UMEC/VI (62.5/25 mcg) OD administered as single inhaler (n=2070)
Outcomes	**PRIMARY:** • Annual rate of moderate or severe exacerbations **SECONDARY (prespecified):** • Change from baseline in trough FEV_1 at wk 52 for FF/UMEC/VI vs. FF/VI; Change from baseline in SGRQ total score at wk 52 for FF/UMEC/VI vs. FF/VI; Time to first on-treatment moderate or severe exacerbation comparing FF/UMEC/VI with UMEC/VI and with FF/VI; • Annual rate of on-treatment moderate and severe exacerbations comparing FF/UMEC/VI with UMEC/VI in patients with eosinophil count ≥ 150 cells/µL; • Annual rate of on-treatment severe exacerbations comparing FF/UMEC/VI with UMEC/VI and with FF/VI
Study Design	Multicentre 3-arm parallel group DBRCT consisting of a 2-week run-in period, up to 52-week treatment period and a 1-week safety follow-up period

There were no significant differences among the 3 treatment groups at baseline with regard to demographics, COPD exacerbations and CAT score (Table 3). The mean age of study patients was 65.3 (8.3) years, 66% were males, and 65% were former smokers. Postbronchodilator FEV_1 was 45.5% of predicted normal value and a mean CAT score of 20.1 (6.1) at screening. Forty seven percent and 26% had a history of ≥ 2 moderate COPD exacerbations and ≥ 1 severe COPD exacerbation, respectively. Patients with a history of asthma were included in the study. Use of specific drugs within the LABA, LAMA and ICS class is not reported. Nearly 40% of the patients were receiving triple therapy, and more than 70% were receiving ICS at randomization. It is not reported whether dual therapy (LAMA/LABA or LABA/ICS) actually failed in those patients receiving triple therapy at screening.

Table 3: IMPACT 2018 baseline characteristics of study participants

	FF/UMEC/VI 100/62.5/25mcg (n=4151)	**FF/VI 100/25mcg (n=4134)**	**UMEC/VI 62.5/25mcg (n=2070)**
Age (years), mean (SD)	65.3 (8.2)	65.3 (8.3)	65.2 (8.3)
Female sex	1385 (33%)	1386 (34%)	714 (34%)
Former smokers	2715 (65%)	2711 (66%)	1342 (65%)
Moderate or severe COPD exacerbations in previous yr			
0	2 (<1%)	5 (<1%)	9 (<1%)
1	1853 (45%)	1907 (46%)	4691 (45%)
2	1829 (44%)	1768 (43%)	4487 (43%)
≥3	467 (11%)	454 (11%)	1168 (11%)
≥2 moderate COPD exacerbations in previous yr	1967 (47%)	1921 (46%)	989 (48%)
≥1 severe COPD exacerbation in previous yr	1087 (26%)	1069 (26%)	515 (25%)
≥2 severe COPD exacerbations in previous yr	147 (4%)	148 (4%)	76 (4%)
CAT score, mean (SD)	20.1 (6.1)	20.1 (6.1)	20.2 (6.2)
Postbronchodilator FEV_1 (% predicted normal value), mean (SD)	45.7 (15.0)	45.5 (14.8)	45.4 (14.7)
COPD medication taken at screening			
ICS + LABA + LAMA	1396 (34%)	1433 (35%)	734 (35%)
ICS + LABA	1103 (27%)	1067 (26%)	523 (25%)
LABA + LAMA	330 (8%)	308 (7%)	163 (8%)
LAMA	273 (7%)	331 (8%)	140 (7%)
ICS + LABA + LAMA + Xanthine	142 (3%)	88 (2%)	67 (3%)
ICS	109 (3%)	109 (3%)	55 (3%)
ICS + LABA + Xanthine	109 (3%)	103 (2%)	51 (2%)
LABA	98 (2%)	105 (3%)	42 (2%)
ICS + LABA + LAMA + PDE4 inhibitors	39 (<1%)	41 (<1%)	21 (1%)
ICS + LAMA	42 (1%)	36 (<1%)	18 (<1%)
LABA + LAMA + Xanthine	23 (<1%)	16 (<1%)	15 (<1%)

Overall, 9087 patients (88%) completed the trial and 7991 (77%) completed the trial while receiving randomized therapy. This study analyzed safety and efficacy data using an intention-to-treat approach, which is a method designed to overcome loss of information due to premature discontinuation of study treatment. However, a full intention-to-treat analysis was not performed because patients who permanently discontinued study treatment did not come in for further evaluation. Patients were encouraged to continue in the study by participating in telephone contacts in order to assess exacerbations, SAEs and concomitant medications post-treatment. However, number of calls completed and the accuracy and completeness of phone call information in those patients who were successfully contacted is unknown. Vital status was available from independent data sources for 9781 (94.4%) of the total study population at Week 52. A summary of patient disposition is provided in Table 4.

Table 4: Patient disposition in IMPACT 2018

	FF/UMEC/VI	FF/VI	UMEC/VI
Randomized	4151	4134	2070
Total withdrawals	758 (18%)	1040 (25%)	566 (27%)
Total adverse events	2897 (70%)	2800 (68%)	1429 (69%)
Withdrawal due to lack of efficacy	163 (4%)	313 (8%)	172 (8%)
Withdrawal due to adverse events	252 (6%)	327 (8%)	187 (9%)
Lost to follow-up	21 (0.5%)	25 (0.6%)	14 (0.7%)

Risk of bias in IMPACT 2018

The Cochrane Risk of Bias tool was used to assess the quality of IMPACT 2018. This appraisal tool highlights both the strengths and weaknesses of included studies. Key elements of trial methodology and reporting are assessed using a standardized set of criteria. If the methods are inadequate there is a "high risk of bias". If the risk of bias is "unclear" usually the trial report did not adequately describe the methods. If the methodology and reporting are adequate there is a low risk of bias. IMPACT 2018 is judged to have a high risk of bias according to the Cochrane Risk of Bias Tool with respect to attrition, selective reporting and source of funding. (Table 5). There are also other biases with respect to study design and the presence of confounding that misrepresent the treatment effect (see Discussion).

Table 5: Cochrane risk of bias summary for IMPACT 2018

Domain	Judgement	Support for Judgement
Random sequence generation (selection bias)	Low risk	"Patients will be randomised using the proprietary RandAll software (GlaxoSmithKline), and assigned to treatment using the Randomisation and Medication Ordering System (RAMOS; GlaxoSmithKline)."
Allocation concealment (selection bias)	Low risk	"The study will use site-based randomization to allocate treatments. Once a randomization number is assigned to a subject it cannot be reassigned to any other subject in the study."
Blinding of participants and personnel (performance bias)	Low risk	"Each regimen was administered in a single dry-powder inhaler (DPI) (Ellipta, GlaxoSmithKline)." "Investigational product…will be double-blinded and will be delivered by DPIs that are identical in appearance. Neither the subject nor the Investigator will know which IP the subject is receiving."
Blinding of outcome assessment (detection bias)	Low risk	"Blinded evaluation of exacerbation rates is planned for this study…"

Domain	Judgement	Support for Judgement
		"All reports of serious adverse events and all trial deaths were adjudicated by an independent adjudication committee whose members were unaware of the treatment assignments."
Incomplete outcome data (attrition bias)	High risk	The intent-to-treat (ITT) population will comprise all patients who are randomized to treatment except for those randomised in error. This is the primary analysis population and will be used for safety and efficacy analyses." "Patients who permanently discontinue study treatment will be encouraged to continue in the study by participating in telephone contacts in order to assess exacerbations, SAEs and concomitant medications post-treatment." **It is important to know how many were contacted and how missing data were handled (e.g. LOCF analysis) for those who could not be contacted but this information is not reported.** "…vital status is available for 9781 (94.4%) of the total study population at Week 52. Data for the remaining 5.6% of patients are currently being sought." **The high withdrawal rates will lead to attrition bias except for mortality data.**
Selective reporting (reporting bias)	High risk	The study publication does not report all outcomes specified in the protocol (e.g. rescue salbutamol use; health care utilization)
Other bias	High risk	"The trial was designed by academic partners and the sponsor (GlaxoSmithKline), which also paid for editorial support; the lead author is an employee of the sponsor."

Outcomes reported

Results are presented in Table 6 according to the outcome hierarchy described above.

Table 6: Hierarchy of outcomes in IMPACT 2018

	FF/UMEC/VI (n=4151)	FF/VI (n=4134)	UMEC/VI (n=2070)
Total mortality (on- and off-treatment)	89 (2.1%) RR 0.91 (0.69,1.21) vs. FF/VI RR 0.74 (0.54,1.02) vs. UMEC/VI	97 (2.4%)	60 (2.9%)
Time to 1st event analysis	HR 0.71(0.51,0.99) p=0.043 vs. UMEC/VI HR 0.90(0.67,1.20) p=NS vs. FF/VI	HR 0.79(0.58,1.10) p=NS vs. UMEC/VI	
Total mortality (on-treatment only)	50 (1.2%)	49 (1.2%)	39 (1.9%)
Time to 1st event analysis	HR 0.58(0.38,0.88) p=0.01 vs. UMEC/VI	HR 0.61(0.40,0.93) p=0.02 vs. UMEC/VI	
Total SAEs	895 (22%)	850 (21%)	470 (23%)
Total hospitalizations	NR	NR	NR
Hospitalization due to severe COPD exacerbation	NR	NR	NR
SAE of pneumonia	184 (4%)	152 (4%)	54 (3%)
Prespecified AE of pneumonia	317 (8%) RR 1.63 (1.31,2.03) p<0.0001 vs. UMEC/VI RR 1.08 (0.93,1.26) p=NS vs. FF/VI	292 (7%) RR 1.51(1.21,1.88) p=0.0003 vs. UMEC/VI	97 (5%)
Number of patients with ≥1 moderate or severe COPD exacerbation	NR	NR	NR
Number of patients with ≥1 severe COPD exacerbation	NR	NR	NR
SGRQ total score – based on subset of 7814 (76%) patients			
Patients evaluated	3318 (80%)	3026 (73%)	1470 (71%)
Change from baseline	-5.5(-5.9,-5.0)	-3.7(-4.2,-3.2)	-3.7(-4.4,-3.0)

	FF/UMEC/VI (n=4151)	FF/VI (n=4134)	UMEC/VI (n=2070)
Difference	-1.8(-2.4,-1.1) p<0.001 vs. FF/VI -1.8(-2.6,-1.0) p<0.001 vs. UMEC/VI		
Patients with ≥4 point decrease (MCID)	1723 (42%) OR 1.41(1.29,1.55) vs. FF/VI OR 1.41(1.26,1.57) vs. UMEC/VI	1390 (34%)	696 (34%)
Time to 1st moderate or severe exacerbation	HR 0.85(0.80, 0.91) p<0.001 vs. FF/VI HR 0.84(0.78, 0.91) p<0.001 vs. UMEC/VI		
Transition Dyspnea Index – based on subset of 5058 (49%) patients Patients with ≥1 unit increase (MCID)	36% OR 1.36 (1.19, 1.55) p<0.001 vs. FF/VI OR 1.33 (1.13, 1.57) p<0.001 vs. UMEC/VI	29%	30%
Use of rescue salbutamol	NR	NR	NR
COPD related health care utilization	NR	NR	NR
Trough FEV_1 – based on subset of 7646 (74%) patients Patients evaluated Change from baseline (mL) Difference	3366 (81%) 94(86,102) 97(85,109) p<0.001 vs. FF/VI 54(39,69) P<0.001 vs. UMEC/VI	3060 (74%) -3(-12,6)	1490 (72%) 40(28,52)

1. Total mortality

There were no differences in the total mortality rates between triple therapy with FF/UMEC/VI and either dual combination.

2. SAEs

There were no differences in total SAEs between triple therapy with FF/UMEC/VI and either dual combination. Hospitalization due to any cause was not reported.

A serious adverse event of pneumonia occurred in 4%, 4%, and 3% of patients treated with FF/UMEC/VI, FF/VI and UMEC/VI, respectively. There was a higher incidence of pneumonia in the groups that received ICS (FF/UMEC/VI and FF/VI) than in the UMEC/VI group.

Time-to-first-event analysis reveals that the risk of clinician-diagnosed pneumonia was significantly higher with triple therapy than with UMEC/VI (HR 1.53; 95% CI, 1.22,1.92). There was no significant difference in the risk of pneumonia between triple therapy and FF/VI.

3. Acute moderate or severe COPD exacerbations

a) A moderate exacerbation was defined as an exacerbation leading to treatment with antibiotics and/or systemic glucocorticoids. A severe exacerbation was defined as an exacerbation that required hospitalization or resulted in death.

> **CRITICAL APPRAISAL ISSUE:** Given that this multicenter trial was conducted in 37 different countries there will be variability in treatment practices of moderate COPD exacerbations across centers that could bias the study findings**.**

b) The number of patients with one or more acute moderate or severe exacerbations was not reported.

> **CRITICAL APPRAISAL ISSUES:** The trial reports the annual rate of moderate or severe exacerbations (pre-specified primary outcome), which was 0.91 per year with triple therapy versus 1.21 per year with the UMEC/VI combination They added all the exacerbations that took place in a treatment arm and divided by the number of years in the study. Therefore, they counted multiple exacerbations that occurred in a single patient. They then created rate ratio with triple therapy, 0.75 (95% CI 0.70,0.81); 25% difference in the annual rate; P<0.001] and 1.07 per year with the FF/VI combination [annual rate ratio with triple therapy, 0.85 (95% CI 0.80,0.90); 15% difference in the annual rate; P<0.001].
>
> Interpreting a 0.25 and .15 reduction in an annual rate is not possible without knowing how to divide the effect among individual people. If this rate reduction was a reduction in the proportion of people who had one or more exacerbation, NNT calculations could be made. With a rate estimate, perhaps this means that a person needs treatment for 4 years with triple therapy to prevent one or more additional moderate to severe exacerbation with UMEC/VI and 6 years versus FF/VI?
>
> The reported rates are also uncertain due to the withdrawal rates in the three groups (18, 25 and 27% in UMEC/FF/VI, FF/VI and UMEC/VI, respectively). It is unclear how annual rates of moderate or severe exacerbations were calculated and whether patients who withdrew prematurely were appropriately accounted for in this calculation. In an effort to reduce bias in the safety and efficacy analysis, the investigators state they tried to collect post-treatment exacerbations, SAEs and concomitant medications data via telephone contacts on patients who prematurely discontinued assigned treatment during follow-up. The success rate as well as the accuracy and completeness of information from these telephone

contacts is not known. This attempt to reduce attrition bias is insufficient without knowing how successful they were at obtaining information via phone contacts

c) Time-to-first-event analysis reported that triple therapy was associated with a lower risk of moderate or severe exacerbations during treatment than dual therapy. The hazard ratio (HR) on the reported study sample for triple therapy versus FF/VI was 0.85 (95% CI 0.80 to 0.91; 15% difference; P<0.001), and versus UMEC/VI was 0.84 (95% CI 0.78 to 0.91; 16% difference; P<0.001).

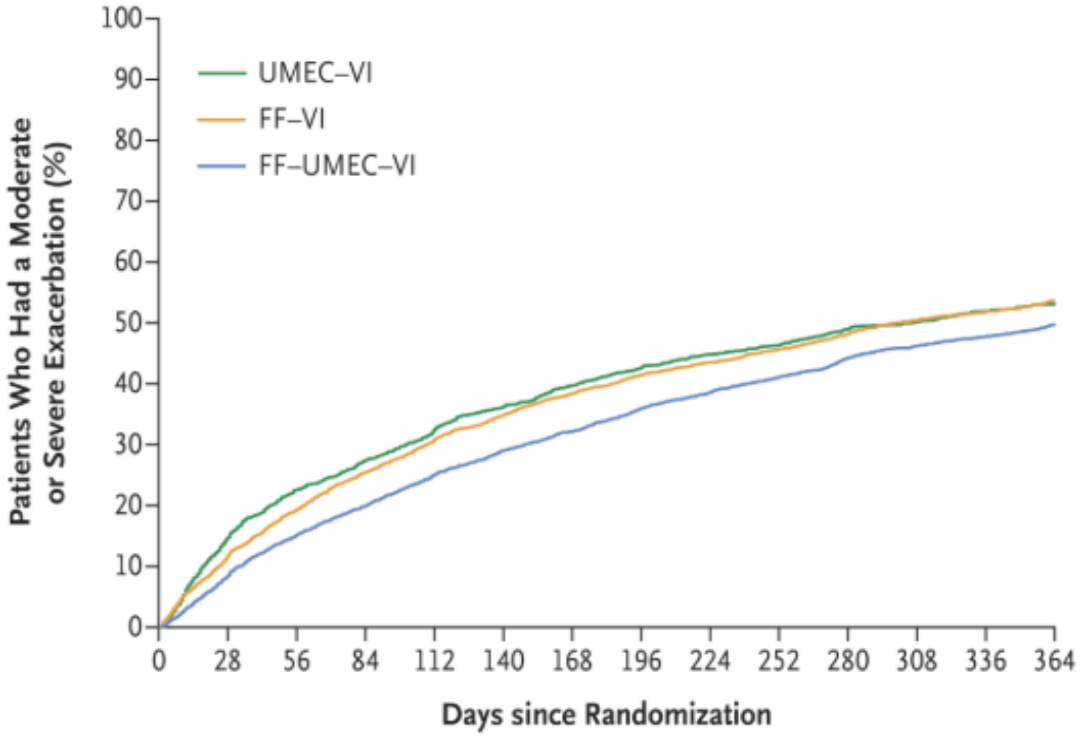
CRITICAL APPRAISAL ISSUE: Time-to-first-event analysis is useful only when it is known how many patients had more than one exacerbation throughout the study in the 3 treatment groups. Time-to-first-event analysis is potentially biased by the increase in exacerbations following abrupt withdrawal of ICS in the UMEC/VI group or UMEC in the FF/VI group.

D) Patients with a history of asthma were included. In addition, nearly 40% of randomized patients were already receiving triple therapy and more than 70% were receiving a COPD regimen that included ICS.

CRITICAL APPRAISAL ISSUE: Sudden FF or UMEC withdrawal at randomization in those patients assigned to dual bronchodilator may explain more rapid increase in exacerbations in these group as compared to triple therapy during the first month of follow-up. The incidence of moderate or severe exacerbations among the 3 groups was similar during the subsequent 11 months of follow-up (Figure 2).

Evidence from double blind, placebo controlled, parallel group RCTs ranging from 26 to 52 weeks duration in patients (N=244-373) with moderate to severe COPD and a history of exacerbations reported that abrupt withdrawal of ICS increased the proportion of patients with one or more severe exacerbations (21,22,23). Of the 244 patients in the 6-month study, 69 (57%) in the placebo (i.e. ICS discontinuation) group and 58 (47%) in the ICS group experienced at least one moderate exacerbation [HR 1.5 (95% CI 1.1,2.1)], defined as worsening of respiratory symptoms that required treatment with a short course of oral corticosteroids or antibiotics (21). In a 1-year pragmatic RCT in 260 primary care COPD patients the relative risk of experiencing a moderate (i.e. requiring oral corticosteroids or antibiotics) or severe exacerbation (i.e. resulting in hospitalization) was greater with placebo versus continued ICS [RR 1.6 (95% CI 1.2,2.2); P<0.001]. (22) The effects of 1-year withdrawal of ICS after a 3-month run-in with ICS/LABA were studied in 373 COPD patients (23).

Figure 2: Time-to-first-event analysis of moderate or severe COPD exacerbations



4. Health-related quality of life

SGRQ was used to measure health-related quality of life in this study. SGRQ total score ranges from 0 to 100, with lower scores indicating better health-related quality of life. A minimum change in score of 4 points is considered as clinically important (i.e. MCID).

Mean change in SGRQ total score was evaluated in 7814 (76%) patients. In this subset of patients there were significant differences between the FF/UMEC/VI group and the FF/VI [-1.8 (95% CI -2.4,-1.1)] and UMEC/VI [-1.8 (95% CI-2.6,-1.0)] groups.

> **CRITICAL APPRAISAL ISSUE:** SGRQ total score was only reported for a subset of 7814 (76%) patients. The finding of improved quality of life with triple therapy is unreliable because data for 24% of patients who withdrew prematurely from the study are missing. Analysis of the effect of treatment on SGRQ total score should be based on all randomized patients rather than incomplete data from a subset of patients.

5. Symptomatic improvement

TDI score was used to measure the severity of dyspnea (breathlessness, shortness of breath) in this study. TDI score ranges from -9 to 9, with a lower score indicating more deterioration in severity of dyspnea. A minimum improvement of 1 point is considered a MCID.

The score was only reported In a subset of 5058 (49%) of randomized patients.

CRITICAL APPRAISAL ISSUE: TDI score was only reported for a subset of 5058 (49%) patients. The finding of symptomatic improvement with triple therapy is unreliable because data for half of randomized patients are missing. Analysis of the effect of treatment on TDI score should be based on all randomized patients rather than incomplete data from 49% of randomized patients.

6. **Use of rescue salbutamol**

Despite being listed as a protocol-defined endpoint, use of rescue salbutamol was not reported in the published study.

CRITICAL APPRAISAL ISSUE: If triple therapy actually improves TDI score, a significant decrease in use of rescue medication is also expected in this group.

7. COPD related health care utilization

This includes physician visits/ER visits and hospitalization. It is another outcome that was not reported in the study publication despite being listed as a prespecified study endpoint in the protocol.

8. Adverse events

a. Adverse events occurred in 2897 (70%) receiving triple therapy with UMEC/FF/VI, 2800 (68%) receiving FF/VI, and 1429 (69%) receiving UMEC/VI. There was no difference between triple therapy and dual therapy comparators for total adverse events.
b. A total of 252 (6%), 327 (8%) and 187 (9%) patients treated with FF/UMEC/VI, FF/VI and UMEC/VI, respectively, withdrew due to an adverse event. There was no difference between triple therapy and dual therapy comparators for withdrawal due to adverse events.

CRITICAL APPRAISAL ISSUE: Overall, 9087 patients (88%) completed the trial and 7991 (77%) completed the trial while receiving randomized therapy. This study analyzed harm data using an intention-to-treat approach, however, a full intention-to-treat analysis was not performed because patients who permanently discontinued study treatment did not come in for further evaluation.

9. FEV_1

In 7916 (76%) patients evaluated, the difference between the triple therapy and FF/VI and UMEC/VI groups in the mean change from baseline in trough FEV_1 was 97 ml (95% CI 85,109) and 54 ml (95% CI 39,69), respectively.

CRITICAL APPRAISAL ISSUE: FEV_1 is a surrogate outcome that has validity in estimating the risk of dying from COPD but little use in assessing the impact of inhaled drug therapy on COPD symptoms.[2}

Reports prepared by independent Groups

Trelegy Ellipta received a European marketing authorisation in November 2017. Health Canada approved Trelegy Ellipta as the first single inhaler triple therapy on April 4, 2018. It was licensed in both jurisdictions for treatment of patients with moderate to severe COPD who are not adequately treated by a combination of an ICS/LABA based on assessments of evidence from studies excluded from this review. (24,25)

The National Institute for Health and Care Excellence (NICE) evidence summary assessed 2 RCTs on the safety and efficacy of Trelegy Ellipta, FULFIL 2017 and IMPACT 2018 (13,20). Only IMPACT 2018 was included in this review. NICE notes that in the IMPACT study there was a statistically significant 15% reduction in the annual rate of moderate or severe exacerbations with UMEC/FF/VI compared with FF/VI but this is less than the 20% relative risk reduction for COPD exacerbations that the NICE COPD full guideline considers to be the minimum clinically important difference. There was also a statistically significant 25% reduction in the annual rate of on treatment moderate or severe exacerbations with UMEC/FF/VI compared with UMEC/VI, however the upper 95% CI crosses the minimum clinically important difference of 20%. NICE also points out that IMPACT 2018 included a 2-week run-in period prior to randomization where participants continued using their current COPD medication (39% of the participants in the UMEC/VI group were previously using an ICS, LABA and a LAMA) and it is unclear whether or not this abrupt cessation of ICS treatment in the UMEC/VI group may have had an effect on exacerbation outcomes. In the FF/VI group, 38% of participants were also using an ICS, LABA and LAMA prior to randomization and so they will have also had a step down in treatment. (26)

Summary

- One study was included: IMPACT 2018, a double blind RCT of 52 weeks duration comparing triple therapy with FF/UMEC/VI (n=4151) with UMEC/VI (n=4134) and FF/VI (n=2070), all administered once daily as a single inhaler, in 10,355 patients with symptomatic COPD and a history of exacerbation within a year before enrolment
- IMPACT 2018 is judged to have a high risk of bias according to the Cochrane Risk of Bias Tool with respect to attrition, selective reporting and source of funding. Therefore the overall quality of evidence is low for all outcomes except mortality.
- There was no reduction in total mortality,
- There was no reduction in total serious adverse events (which includes all cause hospitalization and hospitalization due to severe exacerbation).
- Total adverse events and withdrawal due to adverse events were reported on a subset of total randomized patients similar to efficacy outcomes.
- The risk of clinician-diagnosed pneumonia was significantly higher with triple therapy than with UMEC/VI but not with FF/VI, although reporting for this outcome is also incomplete.

- The claimed benefit of a reduced rate of moderate to sever exacerbations may be solely due to abrupt ICS or LABA withdrawal and needs to be reported as the proportion of patients with one or more exacerbations.
- There is insufficient evidence whether triple therapy improves quality of life or dyspnea symptoms.
- Use of rescue salbutamol and COPD related health care utilization were not reported.

Conclusion

There is insufficient evidence that triple therapy with FF/UMEC/VI provides therapeutic advantage versus dual therapy (FF/VI or UMEC/VI) in terms mortality, total serious adverse events (which includes all cause hospitalization and hospitalization due to severe exacerbation), moderate exacerbations, total adverse events or withdrawal due to adverse events, COPD symptoms or quality of life.

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