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KEY PAPER EVALUATION

Triple fixed inhaled therapy in frequent chronic obstructive pulmonary disease exacerbators: potential advantages for various degrees of airways obstruction

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ABSTRACT

Introduction: Inhaled therapies are the therapeutic mainstay in stable chronic obstructive pulmonary disease (COPD). They are represented by long-acting bronchodilators (anticholinergics or beta2-agonists) and by inhaled corticosteroids, currently available as a monotherapy or as combination therapies in one inhaler. Combinations of anticholinergics and beta2 agonists or beta2 agonists and inhaled corticosteroids are widely used per the prescription guidelines. The advantage of them are related with higher adherence and better acceptability by the patients as compared to both components dosed with individual inhalers. Bronchodilator combinations have also been demonstrated to exhibit a superior efficacy due to their synergistic mechanism of action when compared to either monotherapy. Triple therapies with anticholinergic-beta2 agonist-inhaled corticosteroid have been under investigation over the last few years and recently one such product became available in the EU for the treatment of stable COPD.

Areas covered: The the FULFIL trial (Lung FUnction and quality of LiFe assessment in COPD with closed trIpLe therapy) investigated the efficacy and safety of fluticasone/vilanterol/umeclidinium once daily therapy in COPD patients.

Expert opinion: The results discussed in this paper support the use of this combination in advanced COPD but also in earlier stages in patients with frequent exacerbation. However further and more long-term assessments are required.

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COPD; inhaled therapy; fluticasone furoate; umeclidinium; vilanterol; triple inhaled therapy

1. Introduction

Chronic obstructive pulmonary disease (COPD) is a prevalent respiratory disease with increasing morbidity and mortality worldwide. It is currently treated in stable state with various types of inhalers, some of them producing bronchodilation (either with one pharmacological agent or with a combination) and some of them adding to the former effect the anti-inflammatory one. Such therapies can be currently used alone or in a combined regimen based on various prescribing indications such as the existence of frequent exacerbations, the severity of the airways obstruction, and the existence of a certain disease phenotype. A maximal therapeutic effect with inhaled therapy is thought to be obtained when triple therapy is applied. However, until recently this could only be achieved using two inhalers, and this approach is not always easy to follow by the patient. Therefore triple therapy in one inhaler has been investigated in various forms and trials.

One such study was the FULFIL trial. This was a phase III randomized double-blind, multicentric study which compared the effects of once-daily triple therapy including fluticasone furoate/umeclidinium/vilanterol 100 µg/62.5 µg/25 µg (FF/UME/VI in Elipta Inhaler©) with inhaled corticosteroid (ICS) and long-acting-β2-agonist (LABA) combination represented by budesonide/formoterol 400 µg/12 µg (ICS/LABA: BUD/FOR in Turbuhaler©) which was dosed twice daily. This paper summarizes the results of this study, discusses comparatively its results, and offers a perspective opinion having as a starting point these findings [1].

2. Results

The intention to treat population included 1810 COPD patients, 911 in the FF/UME/VI arm, and 899 in BUD/FOR arm which received the study treatments for 24 weeks. A subset of 430 patients, 210 in triple therapy, and 220 in combination therapy remained with blinded therapy up to week 52 (and was labeled as extension (EXT) population). Inclusion criteria were mainly represented by age at least 40, class D GOLD (FEV1 less than 50% and with CAT score at least 10 or FEV1 more than 50% but less than 80%, CAT score of at least 10 and either at least 2 moderate exacerbations over the last 12 months or at least 1 severe exacerbation during the same period). Patients were excluded if they had asthma overlap syndrome, respiratory tract infection, or severe COPD exacerbation. The two primary endpoints were represented by the changes from baseline in trough FEV1 and by the changes

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from baseline in health status (which was assessed with the Saint George's Respiratory Questionnaire). Secondary endpoints were mainly represented by the proportion of patients with changes from baseline in trough FEV1 or in health status which were clinically meaningful (i.e. amounted at least 100 ml for the lung function or at least 4 units of score decrease for health status). Other secondary endpoints were represented by the changes from baseline in respiratory symptoms (measured with Evaluating Respiratory Symptoms in COPD score, E-RS) and by the proportion of responders (i.e. patients exhibiting clinically significant response in lung function respectively in health status). Safety endpoints were also included. Efficacy and safety were evaluated at week 24 in the ITT population and at week 52 in EXT population.

Mean age was 64.2 years in the FF/UME/VI and 63.7 years in BUD/FOR. The mean FEV1%predicted at baseline was 45.5% for FF/UME/VI and 45.1% in BUD/FOR.

Triple therapy was associated with a statistically significant improvement in the baseline FEV1 as compared to combination therapy (142 ml vs. −29 ml, treatment difference 171 ml, 95% CI 148–194 ml $p < 0.001$). This effect was also maintained in the EXT population (126 vs. −53 ml, treatment difference 179 ml, 95%CI 131–226 ml $p < 0.001$).

Baseline health status was found to be more significantly improved with triple therapy as compared to combination therapy (−6.6 vs. −4.3, treatment difference −2.2, $p < 0.001$) in the ITT population, whereas in the EXT population this difference was not statistically significant.

Proportions of lung function responders were significantly higher with triple therapy in both ITT and EXT populations: 50% versus 41% in the ITT population OR 1.41, $p < 0.01$, respectively, 46% versus 16%, OR 4.69, $p < 0.001$ in EXT population. Proportion of health status responders followed the same trend in both populations 50% versus 41%, OR 1.41 $p < 0.001$ in the ITT population, respectively, 44% versus 33%, OR 1.5 $p = 0.04$ in the EXT population. The study also reported a reduction in the annualized rate (i.e. calculated as if for 12 months) of moderate/severe exacerbations of 35% for the ITT population and of 44% for the EXT population for the triple therapy compared to combination therapy. Triple therapy was associated with greater reductions in symptoms severity at both 24 and 52 weeks.

Safety analysis reported an incidence of on-treatment adverse events for the ITT population of 38.9% for triple therapy and of 37.7% for combination therapy, the adverse events the most commonly reported being nasopharyngitis (7% for the triple and 5% for the combination) and headache (5% and 6%, respectively). Similarly in the EXT population, their incidences were 11% and 10%, respectively, for nasopharyngitis and 8% and 10%, respectively, for headache. COPD exacerbation was most commonly reported with combination in EXT population. Pneumonia was reported in 2% of patients receiving triple therapy during 24-week period and during 52-week period. In patients receiving budesonide + formoterol combination, this was <1% for the 24-week period and 2% for the 52-week period.

The incidences of the serious adverse events in ITT were 5.4% for the triple therapy and 5.7% for the combination therapy. There were 12 deaths, equally distributed in the two therapeutic arms of the study attributed to advanced COPD or to multiple comorbidities.

Incidence of major cardiovascular events was 0.4% in the triple therapy group and 0.8% in the combination therapy group at week 24, respectively, and 2.4% versus 0.9% at week 52 in the extension group.

3. Significance of the results

This study reports the superior efficacy on lung function and health status of triple combination encompassing a long-acting anticholinergic, a beta2-agonist and an inhaled corticosteroid when compared to combination therapy of the latter two classes in patients with advanced COPD or in patients who were frequent exacerbators. The study although not having the most appropriate duration for measuring the dynamics of the exacerbations rate used an appropriate surrogate measure, the annualized rate of moderate to severe COPD exacerbations, that is, those who are the most significant component of the morbidity burden in this disease. Both triple therapy and combination therapy were well tolerated and associated with low incidence of adverse events. There was an extension phase of the study up to 52 weeks which involved a smaller sample (EXT population) randomly selected and with baseline characteristics rather similar to those of the ITT population. Similar efficacy and safety results were found in the EXT sample.

However, the study also enrolled patients with no or with 1 exacerbation during the last 12 months corresponding to class B COPD. The endpoints discussed above were not analyzed according to this classification to better delineate the efficacy of triple therapy strictly in class D COPD patients [2,3]. Such an analysis would have been helpful to demonstrate the potential advantages of a triple inhaled therapy approach in frequent exacerbators with more preserved lung function.

The superior efficacy of the triple therapy (with two inhalers, or open triple) was demonstrated previously but against long-acting anticholinergic component alone: in a 12-week study in which 660 patients were enrolled, budesonide + formoterol added to tiotropium were superior to tiotropium alone in improving lung function, health status, and in reducing exacerbations rate [4].

Subsequently a 52-week study compared the efficacy and safety of (beclomethasone + glycopyrronium + formoterol) versus beclomethasone + formoterol. The triple therapy reduced the incidence of moderate-to-severe COPD exacerbations and improved airflow limitations compared to the double therapy which was demonstrated to produce more modest effects [5].

More recently another fixed triple combination (beclomethasone + glycopyrronium + formoterol) was compared with beclomethasone + formoterol added to tiotropium (open triple) and to tiotropium alone in a 52-week study and it was found that both triple therapies were superior to tiotropium alone in reducing exacerbations rate and in improving lung function [6].

4. Expert opinion

COPD is a disease in which currently many efforts are made to identify new therapies which should be able to produce a

potent and sustained bronchodilation on the one hand and which should significantly reduce the chronic airways inflammation. The existing therapies are not able to reduce this to an extent which should be reflected by a reduced decline in lung function and hence are not able to interfere significantly with disease aggravation. Furthermore some COPD patients have a propensity for more frequent exacerbations despite optimal therapy. Such patients have more severe respiratory symptoms, poor quality of life, and clinically meaningful extra-respiratory symptoms such as fatigue during stable phase [7,8].

The conventional therapy for stable COPD is mainly based on inhaled therapy irrespective of the severity of airways obstruction, the step-up approach actually being used when the existing therapeutic regimen is associated with frequent exacerbations or with disturbing residual respiratory symptoms. This means that if a patient who was started on a long-acting bronchodilator has a suboptimal control of the disease, then another long-acting bronchodilator from a different class should be added. Bronchodilator combinations in one inhaler offer the major advantage of a more facile dosing, a user friendliness of one device as compared to two and consequently a better adherence to therapy. When the bronchodilator combination is not able fully effective and when the number of exacerbations increases, then the addition of an inhaled corticosteroid is necessary. This is currently done most commonly by using one inhaler with long-acting beta2 agonists+inhaled corticosteroid associated to one inhaler containing a long-acting anticholinergic. Only very recently the triple therapy in one inhaler became available in the EU and this means that patients requiring a triple therapy still have to use two inhalers. Most of the investigational triple combinations including the one featured in this analysis are to be used once daily a fact that is again an advantage if the patient has other comorbid conditions and a complex daily therapeutic regimen. One of them which is in fact freshly authorized within the EU (beclomethasone/formoterol/glycopyrronium) is to be dosed twice daily, and this makes it very useful for patients with symptoms which increase in severity during night or early in the morning. The results of this study demonstrate the efficacy of triple combination and enlarge the existing body of evidence demonstrating the need for earlier triple therapy in patients with preserved lung function but who are frequent exacerbators. However, this should be further assessed in subsequent studies enrolling such patients (i.e. with FEV1%predicted 50–80%) and following them up for longer periods.

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Declaration of interest

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