Expert Opinion

Triple inhaled therapy in stable chronic obstructive pulmonary disease: the earlier, the better?

Evaluation of Welte T, Miravitlles M, Hernandez P, et al. Efficacy and tolerability of budesonide/formoterol added to tiotropium in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2009;180:741-50

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Inhaled long-acting bronchodilators (of β_2-agonist or muscarinic antagonist type) or corticosteroids are used in stable chronic obstructive pulmonary disease (COPD) treatment in a step-up approach according to disease severity. Consequently, in more severe disease triple therapy with two bronchodilators and an inhaled corticosteroid can often be encountered in clinical practice, but its short- and long-term effects on disease outcomes are not very well known. The results of a study evaluating the short-term effects of budesonide/formoterol (inhaled corticosteroid/inhaled long-acting β2-agonist combination) and tiotropium (inhaled long-acting muscarinic antagonist) against tiotropium alone are analysed and discussed. On a short-term basis, triple therapy improves lung function, health status and disease morbidity irrespective of disease severity. Long-term benefits of triple inhaled therapy including the effects of its precocious use in less severe COPD subjects should be evaluated.

Keywords: budesonide/formoterol combination, COPD, tiotropium, triple therapy

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1. Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by persistent and progressive airflow limitation with possible exacerbations considered in terms of worsening of symptom intensity [1]. As COPD is recognized as a chronic irreversible respiratory disease, principal goals of its treatment are alleviating symptoms, improving health status, quality of life (QOL) and exercise tolerance, and reducing the future risk of exacerbations [2], that is trying to achieve the optimal control of the disease. Management of stable COPD includes mainly pharmacological therapy and pulmonary rehabilitation.

Different pharmacological options are available in COPD. Bronchodilators are the most important agents [2], and the choice is between long-acting β_2-agonists (LABAs), long-acting muscarinic antagonists and methylxanthines. However, the inhaled route is preferred.

There is evidence that indicates an additive effect on lung function combining a LABA with tiotropium (TIO; the only long-acting muscarinic agent) [3]. In subjects with more severe COPD or a history of frequent exacerbations, the addition of an inhaled corticosteroid (ICS) to a long-acting bronchodilator is recommended [1,4]. Triple therapy with tiotropium, LABA and ICS is widely used in clinical practice.

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Considering the different molecular mechanisms of action of the components, there is a rationale for using these drugs together to obtain better results in the more severe patients, as demonstrated by several studies [5-7].

However, all the studies evaluated the association of TIO to salmeterol and fluticasone. None examined TIO combined to formoterol and budesonide.

2. Methods and results

This was a 12-week, randomized, double-blind, parallel group, multi-centre study enrolling current or ex-smokers with stable COPD [8]. The primary end point was the change from baseline in pre-dose/pre-treatment FEV1 from randomization to full treatment period. Secondary end points were changes from baseline in other lung function (post-treatment FEV1, pre-treatment and post-treatment FVC, pre- and post-treatment, inspiratory capacity (IC), changes from baseline in health status-QOL (Saint George Respiratory Questionnaire; SGRQ). Changes in morning domiciliary FEV1, and PEF (measured pre- and post-treatment), changes in COPD-related symptoms and in the level of morning activities (recorded on an eDiary, assessed with Global Chest Symptoms Questionnaire; and with Capacity of Daily Living during the Morning Questionnaire). Reliever (inhaled short-acting β2-agonist) use was assessed during morning, day, night and overall. COPD exacerbation-related outcome measures were represented by: time to first severe exacerbation and severe exacerbation number (severe exacerbation being defined as COPD worsening requiring systemic corticosteroids and/or hospitalization/emergency room visit). Tolerability as well was assessed throughout the study.

Six hundred and sixty patients were randomized to receive either inhaled TIO 18 μg/once daily and inhaled placebo one inhalation twice daily (monotherapy group, n = 331 patients) or inhaled TIO and inhaled budesonide/formoterol 320/9 μg twice daily (triple group therapy, n = 329 patients). Included in the study were patients with COPD GOLD stage II (25% patients), GOLD stage III (64%) and GOLD stage IV (11%). Both groups were comparable in terms of baseline mean age, gender distribution, lung function nutritional status, time since diagnosis, symptoms scores, mean exacerbations number last year, medications used, etc.

Triple therapy (i.e., TIO/budesonide/formoterol) improved lung function significantly more compared with TIO monotherapy (pre-dose FEV1 mean difference 65 ml, $p < 0.001$; 60 min post-dose FEV1 mean difference 131 ml, $p < 0.001$; pre-dose FVC mean difference 53 ml, $p < 0.021$; 60 min post-dose FEV1 mean difference 160 ml, $p < 0.001$; pre-dose IC mean difference 64 ml, $p < 0.020$; 60 min post-dose FEV1 mean difference 110 ml, $p < 0.001$). Triple combination had a faster onset of its bronchodilator effect compared with TIO monotherapy. Triple therapy exhibited also the largest therapeutic effect on health status compared with monotherapy (SGRQ total score difference 3.8 vs 1.5, $p = 0.023$). Significantly more patients in the triple therapy group exhibited clinically significant (of > 4 units of score) improvements in SGRQ score compared with monotherapy group (49.5 vs 40%, $p = 0.016$). Similar proportions of patients in both groups had clinically significant deterioration in health status (27.6 vs 29.7%). Triple therapy resulted in (significantly) larger improvements in morning domiciliary lung function and daily activities and in significant reduction in reliever use at any time. Triple therapy reduced significantly the severe exacerbations rate/patient/3 months (0.124 vs 0.326, $p < 0.001$), hospitalization/emergency room visits rate/patient/3 months (0.028 vs 0.080, $p = 0.011$); it prolonged also significantly the time to first severe exacerbation/to first hospitalization (HR = 0.39, $p < 0.001$ for severe exacerbation and $p = 0.026$ for hospitalization). Incidence of severe adverse events was comparable in both groups.

3. Discussion

Triple therapy seems to have become routine practice. This is also demonstrated by the fact that approximately 40% of subjects of the present study were already taking triple therapy before enrolment.

This study was aimed to evaluate the effect of a triple therapy (budesonide/formoterol combined with TIO) on lung function, patient-centred clinical outcomes (symptoms, health-related quality of life, exacerbations, and morning activities), and tolerability in patients with COPD.

It demonstrated that, on a short-term basis, triple therapy regimen budesonide/formoterol + TIO improved significantly lung function, COPD-related symptoms, morning activities, health status, reliever use and severe exacerbation outcome compared with TIO alone.

However, the interesting results on exacerbations are influenced by the very strict definition of exacerbation that, differently from many others, did not include also a worsening in symptoms requiring a change or an increase in medications.

Triple therapy regimen unlike TIO monotherapy was associated with an accelerated (faster) overall improvement in pre-dose FEV1 over the study period and with a more rapid and substantial improvement in morning post-dose FEV1 starting with the first week of the study. Budesonide/formoterol combination was previously found to exert similar sustained effects on lung function in studies assessing its efficacy and safety against individual components and placebo: however, if the effects of its components are analysed comparatively, formoterol and not budesonide was found to exert on the lung function (FEV1) beneficial effects, which were larger when compared with placebo, and based on this finding it can be concluded that therapeutic benefit was obtained by adding formoterol to budesonide [9,10].

The study enrolled stable COPD patients with stage II – IV disease, who were randomized to receive either TIO

monotherapy or triple therapy. This means that probably some of the patients with stage II (25% of the enrolled patients) received triple therapy and patients with more advanced disease (stage III – IV) received TIO monotherapy. Overall, the triple therapy regimen was found to be superior to TIO monotherapy on each of the outcome measures considered and this might be due at least in the stage II subset rather to the therapeutic effects of formoterol additional to those of TIO monotherapy than to those of (earlier used) ICS therapy. However, an analysis of efficacy according to disease severity subsets was not performed and therefore this hypothesis cannot be checked against the results.

When analysing the effects on QOL, results showed that approximately 10% more patients receiving triple therapy had a change in SGRQ that exceeded the minimally clinically important difference (MCID) for the SGRQ (i.e., 4 units) compared with TIO monotherapy. This means that, by prescribing triple therapy, it has been possible to increase health status-QOL in a larger proportion of patients.

4. Expert opinion and conclusions

Current therapeutic guidelines recommend that regular inhaled therapy should be initiated in stable COPD stage II with long-acting bronchodilators either β_2-agonists or antimuscarinics, which should be given alone or in combination. Among the long-acting bronchodilators used to treat COPD patients, TIO has demonstrated on both short- and long-term bases the therapeutic effects on lung function (including dynamic hyperinflation), exacerbation rate, health status and disease symptoms. On the other hand, inhaled LABAs have rather been used in COPD combined with inhaled corticosteroids and therefore in more advanced (stage III – IV) disease. Their efficacy as a standalone therapy in less advanced COPD is not clear and, consequently, such compounds are less commonly recommended as monotherapy in milder (stage II) COPD. However, long-term bronchodilator combination (LABAs and muscarinic antagonists) is recommended in such patients to obtain an augmented bronchodilation and reduction of symptoms such as dyspnea. In fact, in the case of TIO/formoterol combination in particular its increased efficacy on lung function and respiratory symptoms is already demonstrated on a short-term basis.

The triple inhaled therapy was demonstrated to be efficacious irrespective of the disease severity stage, but additional long-term data on its effects, especially in subjects with less advanced COPD, are needed in order to document better its uniform efficacy in all COPD stages or its 'selective' efficacy in certain stages.

Declaration of interest

The authors state no conflict of interest and have received no payment in preparation of this manuscript.

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