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Editorial

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Single-inhaler Triple Therapy for Prevention of COPD Exacerbations

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Chronic Obstructive Pulmonary Disease (COPD) is defined by the Global Initiative for Obstructive Lung Disease (GOLD) as a preventable and treatable disease characterized by persistent respiratory symptoms (dyspnea, cough and/or sputum production) and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by exposure to noxious particles o gases [1]. COPD is a high prevalence disease and one of the leading causes of morbidity and mortality worldwide [2].

Exacerbations, defined as acute worsening of respiratory symptoms, mainly dyspnea, that result in additional therapy, are major events in the natural history of the disease that impair quality of life, lung function and are associated with increased mortality [3]. All the exacerbations have a significant impact in heath status but especially moderate and severe. These exacerbations are defined usually in clinical trials as those that need to be treated with antibiotics or systemic glucocorticoids and those resulting in hospitalization or death, respectively.

So, the main treatment goals in the disease include reduction of symptoms and future risk of exacerbation and for this, the key of the pharmacological treatment in COPD patients is the inhaled bronchodilator therapy, that include long-acting β2-agonist (LABA) and long-acting muscarinic antagonist (LAMA) or a combination of both (dual bronchodilation). These long-acting agents are preferred over the short-acting ones, except for patients with only occasional dyspnea [1].

Inhaled triple therapy, consisting of an inhaled corticosteroid (IC), a LABA and a LAMA, and is recommended by the GOLD for patients who have further exacerbations despite dual bronchodilation or a LABA+IC [1].

Recently, single inhalers containing triple therapy (TT) have been developed and offer potential advantages in adherence to treatment and with non-inferiority results in lung function and symptoms compared to the administration of the two inhalers separately [4,5]. Two triple therapy are available or will be soon, in a single inhaler, beclomethasone plus glycopyrronium plus formoterol (BGF) and fluticasone furoate plus umeclidinium plus vilanterol (FUV), and recent clinical trials have been published to assess the effectiveness of these therapies vs LABA+LAMA or LABA+IC for preventing COPD exacerbations.

One of these studies is the TRIBUTE study that compared extrafine single-inhaler triple combination of beclometasone dipropionate, formoterol fumarate, and glycopyrronium, 2 inhalations twice a day versus a single-inhaler dual bronchodilator combination of

indacaterol plus glycopyrronium (IG) one inhalation once a day, being the primary outcome the rate of moderate-to-severe COPD exacerbations over 52 weeks of treatment, in patients with severe or very severe airflow limitation, at least one moderate or severe exacerbation in the previous year, and were receiving inhaled maintenance medication. Before randomization, the patients underwent a 2-week run-in period with one inhalation per day of IG. There was a significant 15% reduction in the rate of moderate-to-severe exacerbations in the TT group compared to the IG group, but without differences if the rates of moderate and severe exacerbations were analysed separately [6]. Moreover, in patients with less than 2% of blood eosinophils per microliter there was no differences in the rate of annual exacerbations between both groups.

The proportion of patients who had adverse events was similar between the two groups, included the risk of pneumonia that was reported by 4% patients in both groups. The other clinical trial, the IMPACT study, compared 52 weeks of a once-daily combination of fluticasone furoate, umeclidinium and vilanterol (FUV) with fluticasone furoate-vilanterol (FV) and umeclidinium-vilanterol (UV). Each regimen was administered once daily in a single Ellipta inhaler. The primary outcome was the annual rate of moderate or severe COPD exacerbations during treatment7. Patients enrolled continued to take their own medication, which could include a LAMA, a LABA, or an IC alone or in combination, during a 2-week run-in period without wash out period before randomization.

The results show that the rate of moderate or severe exacerbations was lower with the TT than with FV (15% of reduction) and UV (25% reduction). The rate of severe exacerbations was significantly lower with the TT than with UV (34% reduction) but not with FV.

The reduction in the rate of moderate or severe exacerbations was lower in the group receiving UV than in the group receiving FV compared with the TT group, what contrasts with the results of the FLAME study [8] were LAMA+LABA demonstrated a significant reduction in COPD exacerbation vs LABA+IC. However, there are some reflexions that we can do about this study [9]. About 822 patients stepped down from TT to UV despite they had had at least one exacerbation in the previous year. This step down could explain the rapid onset in exacerbations observed in the first month after randomization in the UV group. If we analyze all the groups, about 1480 (14, 29% of total population included) patients suffered an abrupt withdrawn of IC. In the TRIBUTE study, patients with TT were excluded from the study that means that there was no step-down in treatment, avoiding this probable increase risk of exacerbations.

Other studies have demonstrated that withdrawn of IC can lead to greater rate of exacerbations, especially in patients with eosinophilia [10]. In the IMPACT study the reduction of the rate of exacerbations with TT vs UV was greater in patients with at least 150 eosinophils per microliter. Moreover, patients with history of asthma were admitted in this study. All these factors could lead to falsely exaggerate the benefit of TT in comparison to the UV.

In the IMPACT study close to 55% of the patients randomized were frequent exacerbators unlike TRIBUTE study where only about 20% of them were frequent exacerbators. GOLD recommends triple therapy for patients of group D who develop further exacerbations on LABA+LAMA or LABA+IC therapy. So, patients included in the IMPACT study fulfill more the profile of patient with indication of TT according to GOLD recommendations.

However, the term of frequent exacerbator based on the number of exacerbations in the previous year is questionable, because it is a characteristic that is relatively unstable throughout the natural history of the disease. Sometimes it is difficult to predict how many exacerbations a patient is going to have basis on the number of exacerbations in the previous year, as was demonstrated in the ECLIPSE study were 41,5% of frequent exacerbators (2 or more exacerbations) reported infrequent exacerbations in the first year of the study and the 40% of frequent exacerbator in the first year reported infrequent exacerbations in the second year of the study [11].

Finally, the incidence of adverse events was similar in all groups, except the incidence of pneumonia that was higher in the IC groups than in the UV group. The rate of pneumonia was significantly higher, more than 50%, with TT than with the UV combination (9.6 vs. 6.1 per 100 patient-years). In the TRIBUTE study the incidence of pneumonia was the same in the TT group as in the IG group. This could suggest that the addition of extra fine BDP to formoterol fumarate and glycopyrronium combination does not increase the risk of pneumonia.

In conclusion, probably in the next months, we will read more about different sub analysis of these important clinical trials, but until further evidence is available, we think that step up to single-inhaler triple therapy will be indicated in patients with more symptomatic GOLD group D with frequent exacerbations after LAMA-LABA regimens, especially with eosinophilia or in asthma-COPD overlap patients with persistent symptoms and exacerbations after LABA+IC therapy.

References

1. Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. http://goldcopd.org/goldreports/ (accessed Apr 29, 2018).
2. Lopez-Campos JL., *et al*. "Global burden of COPD". *Respirology* 21.1 (2016): 14-23.
3. Lopez AD., *et al*. "Chronic obstructive pulmonary disease: current burden and future projections". *European Respiratory Journal* 27.2 (2006): 397-412.
4. Seemungal TA., *et al*. "Exacerbation rate, health status and mortality in COPD--a review of potential interventions". *International Journal of Chronic Obstructive Pulmonary Disease* 4 (2009): 203-223.
5. Bremner PR., *et al*. "Single-inhaler fluticasone furoate/umeclidinium/vilanterol versus fluticasone furoate/vilanterol plus umeclidinium using two inhalers for chronic obstructive pulmonary disease: a randomized non-inferiority study". *Respiratory Research* 19.1 (2018): 19.
6. Vestbo J., *et al*. "Single inhaler extrafine triple therapy versus long-acting muscarinic antagonist therapy for chronic obstructive pulmonary disease (TRINITY): a double-blind, parallel group, randomised controlled trial". *Lancet* 389.10082 (2017): 1919-1929.
7. Papi A., *et al*. "Extrafine inhaled triple therapy versus dual bronchodilator therapy in chronic obstructive pulmonary disease (TRIBUTE): a double-blind, parallel group, randomised controlled trial". *Lancet* 391.10125 (2018): 1076-1084.
8. Lipson DA., *et al*. "IMPACT Investigators. Once-Daily Single-Inhaler Triple versus Dual Therapy in Patients with COPD". *The New England Journal of Medicine* 378.18: 1671-1680.
9. Wedzicha JA., *et al*. "Indacaterol-Glycopyrronium versus Salmeterol-Fluticasone for COPD". *The New England Journal of Medicine* 374.23 (2016): 2222-2234.
10. Suissa S and Drazen JM. "Making Sense of Triple Inhaled Therapy for COPD". *The New England Journal of Medicine* 378.18 (2018): 1723-1724.
11. Watz H., et al. "Blood eosinophil count and exacerbations in severe chronic obstructive pulmonary disease after withdrawal of inhaled corticosteroids: a post-hoc analysis of the WISDOM trial". *The Lancet Respiratory Medicine* 4.5 (2016): 390-398.
12. Hurst JR., *et al.* "Susceptibility to exacerbation in Chronic Obstructive Pulmonary Disease". *The New England Journal of Medicine* 363.12 (2010): 1128-1138.