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Combination long acting β agonists-inhaled corticosteroids *versus* dual bronchodilation: a real conflict?

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Chronic obstructive pulmonary disease (COPD) is a chronic respiratory disease with a relevant epidemiological impact throughout the world.[1]

Acute COPD exacerbations and hospitalizations represent a major burden for patients and health care systems.[2] On the other hand, pharmacologic treatments of stable COPD, while translating into benefits in terms of reduction of exacerbations, may also contribute to social costs, suggesting the importance of appropriate choices in terms of tailored therapy. Recently, new therapeutic strategies for maintenance therapy of COPD, aimed at maximizing bronchodilation by long acting β agonists-long-acting muscarinic antagonist (LABA/LAMA) combinations, have been proposed as an alternative to inhaled corticosteroid/LABA (ICS/LABA) combinations, until now considered the first choice treatment in patients with moderate-to-severe COPD and history of exacerbations.[3]

In this context, some questions need to be addressed: i) should LABA/LAMA combinations be considered an alternative choice to ICS/LABA combinations or should they be targeted to a different phenotype of patient? ii) are we fighting an unnecessary *war* between different types of combined therapy, without considering the possibility of a therapeutic *alliance* in terms of a triple combination?

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In order to stimulate some considerations on the matter, we can start from the pathophysiology of COPD. The working definition of COPD in the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines[4] is based not only on the presence of chronic airflow limitation and comorbidities and the occurrence of exacerbations, but also on the role of chronic inflammation. Actually, a growing presence of inflammatory cells (neutrophils, macrophages, eosinophils, CD4+ and CD8+ cells) has been reported in bronchial airways along with the worsening of the disease, as defined by GOLD stages.[5] Furthermore, the contribution of systemic inflammation to the progression of respiratory impairment is shown by the evidence of an inverse relationship between C reactive protein (CRP) levels and forced expiratory volume in 1 second (FEV1).[6] Therefore, the combination of pulmonary and systemic inflammation may exert a significant impact on the natural history of COPD, leading to hyperinflation, comorbidities and exacerbations.[7] Thus, it is important to take the opportunity to evaluate the impact of different therapies on the specific manifestations of COPD, a multifactorial disease, where, if the airflow limitation is the overall container, systemic and lung inflammation constituting a central core connected with bronchoconstriction, mucociliary dysfunction and structural changes linked to airway remodeling and emphysema.[8] How have these considerations influenced the evolution of the guidelines in the last years? In 2001 the first version of the GOLD guidelines was published,[9] followed by a revision six years later.[10] In previous GOLD documents, recommendations for management of COPD followed primarily a FEV1-centric vision of COPD, being based solely on spirometric category.[11] However, due to raising awareness that FEV1 is only a partial descriptor of disease status, the 2011 revision of the GOLD document adopted a new clinical approach based on a combined assessment of the degree of obstruction, grading of symptoms and rate of exacerbations, thus reserving short-acting bronchodilators in stage A, LABA or LAMA in stage B, ICS/LABA or LAMA in stage C and finally ICS/LABA and/or LAMA in stage D. In patients at high clinical risk of group D, GOLD

2011 guidelines also rank the possibility of a triple therapy as evidence B, as confirmed by a recent meta-analysis.[12] The clinical risk emerges as the main driver in the choice of an ICS/bronchodilator combination.

But which kind of evidence supports this approach?

As considering LABA/ICS fixed combinations, the TORCH study demonstrated in a total of 6112 patients that salmeterol/fluticasone induces a significant reduction in moderate-to-severe exacerbations, including those requiring systemic steroids, in comparison with placebo and single components. A numerically modest increase of pneumonia has also been observed, which was not correlated with an increased mortality.[13] In a *post hoc* analysis of the TORCH study, the clinical benefits of salmeterol/fluticasone were confirmed across all GOLD stages, and in GOLD 2 a significant reduction in mortality of 33% was also obtained.[14] Moreover, in the TORCH study patients treated with salmeterol/fluticasone for 3 years showed a lower incidence of cardiovascular events compared with the control group.[15] Relatively to lung inflammation, salmeterol/fluticasone combination has been demonstrated to induce a significant reduction in CD8+ cells (P=0.015) in bioptic specimens of the bronchial mucosa.[16] Taken together, the significance of these findings can be synthesized in a very favorable number needed to treat (NNT) to prevent exacerbations and hospitalizations (4 and 32 respectively at 1 year), which compares favorably with those observed with other extensively used drugs, such as statins (NNT 50 at 5 years for the prevention of a cardiovascular events).[17] The importance of inhaled corticosteroids has also been confirmed in withdrawal studies. In the COSMIC trial, withdrawal of fluticasone in patients with moderate-to-severe COPD treated for 3 months with the combination salmeterol/fluticasone caused an acute and persistent deterioration in lung function (about –50 mL mean FEV1 at 1 year) and onset of symptoms.[18] GLUCOLD study has shown that the withdrawal of fluticasone is associated with a reactivation of airway inflammation (increase/reappearance of CD3+, CD8+ and mast cells at lamina propria level) and a significant deterioration of clinical symptoms.[19] To mimic an old saying, the slogan *where there is inflammation there is inhaled steroid* could be coined.

About LAMA, in the UPLIFT study tiotropium had significantly delayed in a total of 5993 patients the onset of the first exacerbation of four months compared to controls, reducing the total number of exacerbations per patient/year.[20]

Consequently, a comparison of salmeterol/fluticasone *vs* tiotropium in reducing the rate of exacerbations was conducted in 1323 patients enrolled in the INSPIRE study.[21] The results do not show any significant difference in the overall rate of exacerbations. There were fewer episodes requiring oral corticosteroid treatment in the salmeterol/fluticasone group compared with the tiotropium group (P=0.039), while tiotropium significantly reduced exacerbations requiring antibiotics with respect to salmeterol/fluticasone (P=0.028). As secondary endpoint, a significantly lower drop-out in the group treated with salmeterol/fluticasone compared with tiotropium (34.5% *vs* 41.7%, P=0.005) was reported from the 13th week until the end of the study. Salmeterol/fluticasone also determined, with respect to tiotropium, a significant reduction in mortality, particularly due to cardiovascular events, although, on the other hand, a greater incidence of pneumonia was observed.

Overall, these findings do not absolutely support the extended use of ICS/LABA combinations to all types of patients. In the TORCH study, for example, the decrease in exacerbations did not result in a significant reduction in mortality, since this endpoint, although with an immediately upper limit (P=0.052), was not achieved. Moreover, ICS/LABA combinations do not seem to provide benefits in the treatment of the *emphysema phenotype*, where significant improvements in FEV1 and dyspnea have not been observed.[22] How to bridge this gap? Could dual bronchodilation therapy bring additional benefits *vs* monotherapy in terms of improvement of symptoms, quality of life and lung function? Is dual bronchodilation, with respect to regimens containing inhaled steroids, playing a role of antagonist or could rather become a potentially allied?

Since the first version, a GOLD statement claims that the combination of bronchodilators with different mechanisms of action improves the efficacy and reduces the risk of side effects. Moreover, there are several data supporting synergistic effects shared by LAMA and LABA. Anticholinergics inhibit M2 and M3 muscarinic receptors, which respectively promote bronchoconstriction by Gq11 protein and limit bronchodilation by Gi protein, whereas β2-adrenoceptors exert a direct effect of bronchodilation by Gs protein. Both pathways finally lead to relaxation of respiratory smooth muscle through cAMP- and cGMP-dependent protein kinases.[23] Furthermore, *in vitro* data supporting the benefits of the combination of muscarinic antagonists and β2 agonists in comparison with single agents include: i) a better down-regulation of endothelin-1 expression on lung fibroblasts, leading to a reduction of the muscarinic profibrotic effects;[24] ii) a significative reduction in the neutrophilic inflammatory transforming growth factor β-mediated response in the sputum supernatants from patients with COPD.[25] Finally, muscarinic and β2adrenergic receptors have a different distribution at bronchopulmonary level.[26]

On the basis of these findings, pharmacological research is not only studying new β agonists or anticholinergic agents, but also new fixed combinations between them. In the INTRUST study (1131 patients totally) the addition of indacaterol to tiotropium for 12 weeks significantly increases the inspiratory capacity throughout 24 h and improves symptom control compared to single components, as reported by patients in terms of rescue treatment, intensity of cough and sputum characteristics. Tolerability was similar between treatment groups in terms of both total and serious adverse events, particularly at cardiac conduction level.[27]

In the 26-week SHINE study, a fixed combination of indacaterol/glycopyrronium compared to single components and tiotropium showed in a total of 2144 patients that FEV1 at the 24th h was significantly better, without reaching the minimum threshold of clinical significance, and with adverse events comparable to placebo.[28,29] In the 64-week SPARK study, the combination of indacaterol/glycopyrronium was more effective than single components in a total of 2205 patients on all exacerbations, the rate of which was largely driven by the reduction in the high number of mild exacerbations (self-managed by the patients with rescue medication); for moderate/severe exacerbations the difference was significant only *versus* glycopyrronium but not *versus* tiotropium (P=0.096), whereas no difference between indacaterol/glycopyrronium and single components was observed for severe exacerbations.

As for quality of life, Saint George respiratory questionnaire (SGRQ) score was significantly better in the group treated with the fixed combination, with a higher percentage of patients achieving the improvement of at least 4 units, although only up to week 52.[30]

Taken together, INTRUST, SHINE and SPARK studies deserve some considerations. Firstly, the wide use of ICS in more than half of enrolled patients (up to 75% in the SPARK study) suggests that results may reflect the effects not only of double bronchodilation but rather of a triple therapy ICS/LABA/LAMA. Secondly, the selection of a COPD population with a remarkable bronchodilator reversibility suggests the possibility of an *asthma-COPD overlap syndrome* phenotype in most of these patients, in which we are not yet able to assess the risks of a single bronchodilator treatment in the medium/long-term period.

Finally, could dual bronchodilation play a role in management of the frequent-exacerbator phenotype of COPD? With regard to this aspect, the results of the ILLUMINATE study may provide a partial answer.[31] In this 26-week study comparing indacaterol/glycopyrronium combination once daily *versus* salmeterol/fluticasone combination twice a day on 523 moderate to severe patients without a history of exacerbations, a significant increase in FEV1 AUC 0-12 h was observed in the group treated with indacaterol/glycopyrronium with respect to salmeterol/fluticasone, which however was not accompanied by a clinically significant improvement in the quality of life.

Thus, in this low-risk population of COPD patients, maintenance treatment with two long acting bronchodilators offers benefits compared with ICS/LABA in terms of improvements in lung function. However, a clinically important issue, not addressed by these studies, is the relative efficacy of LABA/LAMA combinations compared to ICS/LABA combinations in COPD patients with moderate-to-severe obstruction or with a history of exacerbations.[3]

Another issue is the therapeutic potential of a triple combination ICS/LABA/LAMA in patients with severe COPD not adequately responder to LABA/LAMA or LABA/ICS. As a matter of fact, evidences are now available supporting the benefits of a triple therapy in some patients, favoring the view of an alliance, rather than a conflict, between these combinations.

The first evidence comes from a 52-week trial in a total of 449 patients with moderate-to-severe COPD treated with salmeterol/fluticasone plus tiotropium.[32] The triple combination did not statistically reduce COPD exacerbations but improved lung function, quality of life and the rate of hospitalizations compared to tiotropium alone, while the combination of the two bronchodilators tiotropium and salmeterol achieved only in part these objectives. In the CLIMB trial (660 patients),[33] the use of triple combination formoterol/budesonide plus tiotropium for 12 weeks lead to a reduction in the number of severe exacerbations by 62% compared to tiotropium alone (P<0.001), while considering emergency room visits and hospitalizations a reduction of 65% was observed (P=0.01). A Scottish retrospective study on a total of 2853 patients[34] showed that the combination tiotropium/ICS/LABA, compared with ICS/LABA alone, significantly reduced mortality from all causes (P<0.001) as well as exacerbations in terms of both rescue therapy and hospitalizations. Finally, a recent meta-analysis of 6 trials over 1200 patients with COPD[12] confirms that triple therapy salmeterol/fluticasone/tiotropium compared to tiotropium alone significantly improves lung function, quality of life and exacerbations without increasing adverse events.

On the basis of these findings, the question is whether different COPD phenotypes, in terms of clinical manifestations and pulmonary imaging of emphysema-predominant or airways disease–predominant findings, should be targeted with different therapeutic approaches. Current evidence suggests dual bronchodilation as a second-line treatment, with a possible use as a first line therapy only in patients with marked dyspnea. Duration of

therapy would be modulated according to symptomatic effects, without pursuing objectives of maximized treatment in order to limit exacerbations or improve functional parameters, moreover carefully monitoring cardiovascular safety and potential risks of on top of prescription.

In my opinion, it is much more important to define the type of patient for which the treatment with inhaled steroid in combination with bronchodilators is appropriate. From the available evidences, ICS/LABA combination shows the best results in patients with moderate or severe obstruction, with frequent exacerbations, with overlap syndrome, in the presence of cardiovascular comorbidities. In contrast, the emphysema phenotype without exacerbations does not seem to receive clinical and functional benefits from inhaled steroids. In patients with severe COPD not adequately responding to LABA/ICS or LABA/LAMA, the opportunity of a triple combination therapy should be considered.

In conclusion, in order to answer the original question, no conflict between LABA/ICS and dual bronchodilation seems to stand out, but rather a different place in therapy in different types of COPD patients, or even an alliance in form of triple combination in patients with more severe disease.

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