Pneumologia
REVISTA SOCIETĂȚII ROMÂNE DE PNEUMOLOGIE

Bronchodilators or combination of long acting beta 2 adrenergic and inhaled steroids: another competition in the future?!

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If we are looking into the real problems of chronic obstructive pulmonary disease (COPD) we can find out many current problems unsolved at this moment: it's a prevalent major medical problem, underdiagnosed, unrecognized, untreated. The current therapies also have their own problems. Monotherapy with bronchodilators is sometimes not sufficient, combinations of different classes of bronchodilators sometimes have not well defined indications and the combination of bronchodilators and inhaled corticosteroids (ICS) is more criticized every day. If we are thinking also that the opinion leaders are speaking more and more about personalized treatment, the puzzle of diagnosis and therapy of COPD is becoming more difficult. We know that regular therapy with long-acting bronchodilators (LABA: long-acting beta-adrenergic agonists; LAMA: long-acting antimuscarinic agents) improves lung function, dyspnoea and quality of life in symptomatic patients with spirometric evidence of airflow obstruction[1,2]. As a consequence of different studies concerning long-acting bronchodilators, was added the effect on reducing the rate of exacerbations, probably due to a reduction in pulmonary hyperinflation and a resetting of lung function dynamics[3]. In the same time, even if updated GOLD is very restrictive for stage C and D patients, the combination of LABA and ICS was overprescribed[4,5] in patients with FEV1 > 50% predicted and history of less than 2 exacerbations per year, despite the well known significant adverse effects[6], particularly regarding an increased risk of pneumonia.

It's an explosion of combinations of LABA and LAMA (with almost 4 different types of association) and the competition with LABA and ICS becomes more evident. The unanswered or partially answered questions are now:

- when we can stop the ICS?
- is the withdrawal from ICS safe?
- when and where we can replace LABA plus ICS with LABA and LAMA?
- can we speak about a real step down in COPD, or it's only an over treated sample of patients with LABA and ICS?
- is it better to start with the combo of bronchodilators or with LABA and ICS?

We try to find an answer to all these questions. Clinicians seem more confident in keeping patients on ICS rather than withdrawing it[2,7], even though it can be regarded as a form of overtreatment[8] and hence inappropriate according to guidelines. The Optimo[3] real-life, prospective study shows that withdrawal of ICS (substituted with indacaterol, one of the bronchodilators) in symptomatic COPD patients with moderate airflow limitation, i.e. FEV1>50% predicted, and no history of frequent exacerbations, i.e. having suffered less than 2 exacerbations in the year prior to the study, was not associated with any deterioration in symptoms, lung function, and exacerbation rate during six months of observation. This study confirms that in COPD patients (with moderate-to mild airflow obstruction, classified as patients B in the new GOLD categories) for whom ICS are not recommended by international documents and guidelines can be safe provided that the patients remain on regular treatment, for the most part with long-acting bronchodilators. Regular treatment with ICS is not needed in COPD patients who are at low risk of exacerbations. Optimo[3] was a study on low risk COPD patients. In COSMIC, a randomized study over 1 year in patients with FEV1 <50% and 2 or more exacerbations, they found that the switch from the fluticasone/salmeterol combination to salmeterol alone resulted in persistent deterioration of lung function and dyspnoea and in an increase in mild exacerbations, while there was no significant difference for moderate-to-severe exacerbations[9]. At the opposite, the randomized controlled INSTEAD study took this a stage further and found no increased risk of exacerbation in patients without prior exacerbations who had less severe lung function impairment when a once-daily long-acting beta 2 -agonist (indacaterol)[10] was used as maintenance therapy.

Historically looking to the comparison of ICS-LABA versus monotherapy with LABA, even if the large TORCH trial failed to conclusively show a difference in mortality between ICS-LABA treatment and placebo[11], more recent database studies suggest that such an effect may be present in a "real-world" population of older patients treated with LABA alone[12]. Another signal comes from the early observational studies suggesting that simply stopping therapy with ICS increased the risk

of exacerbations[13]. It remains the question: the new LABA are really changing the strategies in withdrawing the ICS in COPD patients? Another question is: combining LABA and LAMA can define more accurately the new strategies of withdrawal of ICS? In the Wisdom study (12-month, double-blind, parallel-group research) in patients with severe COPD (FEV1 less than 50% and a history of at least one documented exacerbation in the 12 months before screening) receiving tiotropium plus salmeterol, the risk of moderate or severe exacerbations was similar among those who discontinued inhaled glucocorticoids and those who continued on glucocorticoid therapy[14]. However, there was a greater decrease in lung function during the final step of glucocorticoid withdrawal. Criticized by Suissa and Rossi[15,16] who suggest that the study methodology might be improved. They recommend that patients should be receiving ICS for an extended period before entering a withdrawal trial rather than the 6 weeks of intensive therapy used in WISDOM study (although 70% of WISDOM participants were using ICS at study entry). They proposed also that it is useful to know why ICS treatment was selected initially and then group patients accordingly. Extending the period of follow up will help also after the opinion of the authors[15,16] to resolve some of these issues, especially concerns about the risk of more serious exacerbations among patients where ICS are stopped.

We assist meanwhile to the launch of new combo of bronchodilators which are now in open competition with LABA /ICS. Every month brings more evidence for this type of association. The Energito study, a Phase IIIb, randomized, double-blind, double-dummy, 4-period crossover trial evaluating lung function after 6 weeks of treatment with Tiotropium and Olodaterol (T and O) -O 2.5/5 or 5/5 µg QD versus Fluticasone +Salmeterol (SFC) 250/50 or 500/50 µg BID demonstrate for GOLD 2. T+O significantly improved FEV1 AUC0–12 response and all other FEV1 endpoints compared to F+S[17]. This study suggests[17] that using LABA/ICS, F+S in this study, in moderate/severe COPD may provide sub-optimal lung-function improvements compared to T+O. Another study -Lantern[18] a 26 weeks double-blind, double-dummy, parallel-group study, including 744 patients with moderate-to-severe COPD with a history of ≤1 exacerbations in the previous year randomized (1:1) to QVA149 110/50 µg once daily or SFC 50/500 µg twice daily, support the use of the LABA/LAMA, QVA149 as an alternative treatment, over LABA/inhaled corticosteroid in the management of moderate-to-severe COPD patients (GOLD B and GOLD D) with a history of ≤1 exacerbation in the previous year. QVA149 demonstrated statistically significant superiority to SFC for trough FEV_1 (treatment difference [Δ]=75 mL; P≤0.001) and also significantly a reduced rate of moderate or severe exacerbations by 31% (P=0.048) over SFC. The LANTERN study[18] confirms the potential of QVA149 as a treatment option for symptomatic COPD patients with a history of ≤ 1 exacerbation offering additional benefits over LABA/ICS combinations. And this example was not singular. The Illuminate study[19] a multicenter double-blind, double-dummy, parallel-group study, covering 523 patients (age 40 years or older, on stages II–III GOLD, without exacerbations in the previous year) demonstrate over 26 weeks the QVA 149 110/50 µg superiority versus SFC (treatment difference 0.138 L; 95% CI 0.100–0.176; p<0.0001) with significant symptomatic benefit. These results indicate the potential of dual bronchodilation as a treatment option for non-exacerbating symptomatic COPD patients.

But things didn't stop here. A study just finished, FLAME study, a randomized, double-blind, parallel-group, non-inferiority, active-controlled for 52-weeks, involving 3,362 COPD patients, demonstrated that Ultibro Breezhaler 110/50 mcg[20] was non-inferior to salmeterol/fluticasone (SFC) 50/500 mcg in terms of rate of all COPD exacerbations (mild/moderate/severe) during the 52 weeks of treatment. Secondary endpoints for the study comparing Ultibro Breezhaler to SFC included superiority in terms of rate of all COPD exacerbations over the study duration and efficacy in terms of the following: time to first COPD exacerbation (mild/moderate/severe); rate and time to first moderate-to-severe COPD exacerbation; lung function (trough FEV1); health-related quality of life (as measured by the shortened version of the St George's Respiratory Questionnaire [SGRQ-C]); rescue medication use and safety. It seems that the competition between the combination of LABA and LAMA and the LABA/ICS is open not only for the classical A and B stages with low risk of exacerbation but also for the severe COPD with high risk of exacerbations. Every study has some limits but respecting these criteria important for research (of one year of surveillance) the lessons for the clinicians are:

- it is an overuse of ICS without respecting the stages of GOLD classification
- if the patient had exacerbations but is clinically stable then ICS can be stopped[16] and replaced with monotherapy or better dual therapy of LABA and LAMA
- it's easier to start a ICS therapy and harder to stop it
- even if it exists the first signal on replacing in severe COPD patients with high risk of exacerbations on LABA and ICS with LABA/LAMA we need more studies
- we need probably to define more precisely the group, the phenotype of patients who can support this transition on combo of bronchodilators from LABA/ICS

Finally, I think that the step down is not real. It's more on symptoms based but the future can bring another "revolution" if we are looking to the other competition of different types of LABA/LAMA combinations and the old surviving molecules of LABA/ICS. ■

The author declares no conflict of interest concerning this article

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