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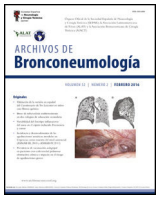

Editorial

The Future of Triple Therapy in Chronic Obstructive Pulmonary Disease☆

Futuro de la triple terapia en la enfermedad pulmonar obstructiva crónica

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The pharmacological treatment of chronic obstructive pulmonary disease (COPD) focuses on 2 main objectives: controlling symptoms (in the form of reduced symptoms, improved exercise tolerance, and better quality of life) and reducing future risk (understood as reduced frequency and severity of exacerbations, improved long-term prognosis, and modification of lung function decline).[1,2] If a drug is to be approved by the regulatory authorities for COPD, it must be effective in at least some of these areas.

Inhaled drugs used in COPD can be combined in various ways to increase their clinical efficacy, without increasing side effects. Several options are available, but the most widely used in Spain is the association of a β2-adrenergic agonist (LABA) with a long-acting muscarinic antagonist (LAMA) and an inhaled corticosteroid (ICS). This combination is known as triple therapy (TT).[3] National clinical practice guidelines (GesEPOC) and international recommendations (GOLD) both advocate the use of TT in patients presenting frequent exacerbations despite treatment with 2 bronchodilators, or in those who present features of asthma-COPD overlap (ACO), but do not achieve control with a combination of LABA/ICS.[1,2] This combination can currently only be achieved in Spain by using 2 inhalers, one containing a LAMA, and the other containing a LABA/ICS combination. Until recently, however, evidence supporting its use was based only on a very few, albeit well-designed, studies.[4]

Three TT combinations in single inhalation devices are currently being developed: beclomethasone/formoterol/glycopyrronium, fluticasone furoate/vilanterol/umeclidinium, and budesonide/formoterol/glycopyrronium. To date, the only published results on TT are from the combination of beclomethasone/formoterol/glycopyrronium compared to tiotropium[5] (TRINITY study) and beclomethasone/formoterol[6] (TRILOGY study), both 52 weeks in duration, and a 24-week trial of the triple combination of fluticasone furoate/vilanterol/umeclidinium, with a 52-week extension in a patient subgroup, compared to budesonide/formoterol[7] (FULFIL study). Clinical trials with beclomethasone/formoterol/glycopyrronium show that TT is superior to both LAMA monotherapy (tiotropium) and to combined treatment with LABA/ICS (formoterol/beclomethasone) in terms of lung function, improved symptoms, and quality of life. Furthermore, both studies showed statistically significant reductions in the rate of exacerbations with the TT (about 20% in both cases) than the comparators. Outcomes compared to tiotropium appear to be dependent on eosinophil levels in peripheral blood and the presence of more than one exacerbation in the previous year, while outcomes from the comparison with formoterol/beclomethasone are more significant in patients with more than one exacerbation in the previous year, irrespective of the eosinophil count. This combination showed a good safety profile in both studies, with a similar profile to the comparators, and no substantial increase in the rate of pneumonia, an effect often associated with the use of ICS. Another interesting aspect of the TRINITY study is that one of the treatment arms received TT in 2 devices (beclomethasone/formoterol in one device and tiotropium in the other), which is the current mode of administration, and both TTs (open and fixed) showed a similar efficacy. The most common side effects were nasopharyngitis (6% in TRILOGY and 5% in TRINITY). In both studies, the rate of serious adverse effects, around 15%, was similar in all treatment arms.

The message emerging from the recently published results of the FULFIL study, a randomized clinical trial comparing fluticasone furoate/vilanterol/umeclidinium with budesonide/formoterol, is very similar to that of the TRILOGY and TRINITY studies: TT is superior to the combination of LABA/ICS in terms of lung function and improvement of dyspnea (44% reduction in the risk of moderate and severe exacerbations compared to the comparator), and has few side effects, the most common being nasopharyngitis and headache (11% and 8%, respectively).

These data give us some insight into the future of TT in the treatment of COPD, although the most important question remains unanswered: what is the benefit of TT over dual bronchodilation (LAMA/LABA) in the control of symptoms and the prevention of exacerbations? According to current data, the benefit of ICS in preventing exacerbations appears to depend on evidence of

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Th2 inflammation (expressed as elevated levels of eosinophils in peripheral blood), so TT may only be superior to dual bronchodilation in the prevention of exacerbations in patients who are currently considered to have ACO (asthma-COPD overlap), or those who present features suggestive of ACO, such as eosinophilia or raised levels of nitric oxide in exhaled air (FeNO).

With this in mind, we are awaiting with interest the results of 3 ongoing 1-year clinical trials comparing triple therapy with dual bronchodilation as the current gold standard,[8–10] all of which investigated the annual rate of moderate and severe exacerbations among the study groups as their primary objective. As well as examining the overall results of these studies, we will also have to closely look at patient data in order to define the COPD patient population that might best benefit from this therapy.

It seems likely that the new evidence and new treatment options will compel us to urgently revise the therapeutic recommendations for some COPD treatment groups, taking into account concepts such as disease control, as was the case in asthma.

In summary, TT will be the future choice of treatment for a certain group of COPD patients, probably those currently defined as ACO. It remains to be seen if this treatment is sufficiently effective to be recommended in any other patient group.

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