



Editorial

Arguments Against Inhaled Glucocorticoids in COPD by Phenotype Instead of by Severity^{☆,☆☆}

Glucocorticoides inhalados en la EPOC por fenotipo en lugar de gravedad.

Argumentos en contra

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Before entering into the debate created by the title proposed by the Editorial Committee of *Archivos de Bronconeumología*, I believe it is essential to establish three previous considerations. The first is in reference to the use of glucocorticoids in stable COPD. Currently, and after the results of the Towards a Revolution in COPD Health (TORCH)¹ assay, it is difficult to recommend their continuous use in an isolated manner (monotherapy) without associating at least one long-acting beta-agonist bronchodilator, either separately or combined in the same device. From the perspective of therapeutic efficacy as well as from that of safety, the TORCH assay shows that the combination of an inhaled glucocorticoid with a long-acting beta-agonist is always better than the individual use of these two components. The second consideration is the term “phenotype”, understood as those structural and functional characteristics observed in an organism that are modulated by interaction with the genotype and setting.² The third and last is the word “severity”, which in stable COPD should be contextualized within the framework of the clinical data and the spirometric anomalies.

Having set these three premises, I will center the debate within the context of the Global Initiative for Chronic Obstructive Pulmonary Disease (GOLD). Starting with the first version of the Executive Summary in 2001³ and later in the second from 2007,⁴ the GOLD proposal has coherently defended a series of suggestions related with the management and treatment of stable COPD. These are based on the principle that the clinical approach and pharmacologic treatment of COPD (aside from exacerbations) are characterized by a staggered increase of the medication depending on the severity of the disease and its response to the individual therapeutic possibilities of each patient. And it indicates that the severity of the disease is determined by the relevance of the symp-

toms that the patient presents and also by the limitation of the airflow, a fundamental physiopathological feature in COPD. Other important elements that should be kept in mind should be the frequency and the severity of the exacerbations, the coexistence of comorbidities (cardiovascular disease, diabetes mellitus, psychiatric disorders, sleep disorders, etc.), the presence of respiratory failure and, of course, health-related quality of life. Last of all, it insists that the therapeutic management also depends on the educational level and the motivation of the patients to adapt to the recommended regime, without forgetting the socio-cultural setting, environmental circumstances and the availability of the medication. All these factors are reinforced by the main objectives that should always be our goal: the prevention and control of symptoms, reduction of exacerbations, frequency and severity, improved state of health and optimized tolerance to physical effort. It also categorically states that none of the existing COPD medications is able to reduce the fall in lung function (FEV₁) in the long-term (evidence A), another of the important characteristics of the disease. Nevertheless, this statement should not lead to the exclusion of any of the preparations available in the current therapeutic armamentarium.

For symptomatic patients with severe or very severe COPD (GOLD 3 and 4), the 2007 version⁴ recommends the regular use of one or more long-acting bronchodilators: long-acting beta-agonists (e.g. formoterol and salmeterol, and since this year, indacaterol⁵) and/or the anticholinergic tiotropium bromide, combined with pulmonary rehabilitation and inhaled glucocorticosteroids if the patient has associated symptoms and presents repeated exacerbations (evidence A). And it underlines some key points. Regarding bronchodilators, it insists that these are the main medications for the symptomatic treatment of COPD (evidence A) and that they may be administered, on occasion, as rescue for the immediate relief of symptoms (short action), or regularly to prevent or reduce these symptoms (long action). Referring to the different types of bronchodilators for the treatment of COPD, the selection should be based on the availability of the medication and on the individual patient response. It also highlights that all bronchodilators optimize the capacity for physical effort, without being accompanied by

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significant changes in FEV₁ (evidence A). The combination of different bronchodilators, with their different mechanisms of action and duration of effects, can improve the bronchodilator effect without the side effects worsening necessarily. As for inhaled glucocorticoids, it is highlighted that their prolonged use does not modify the progressive fall in lung function (FEV₁) (evidence A). A previous recommendation,³ their indication in moderate COPD patients (GOLD 2) that associate a significant bronchodilator response, was abandoned given the high frequency and little relevance, as demonstrated in the therapeutic assay “Understanding potential long-term impacts on function with tiotropium” (UPLIFT).⁶ In any case, it insists that long-term use of systemic glucocorticosteroids is not recommended under any circumstances in COPD (evidence A) due to its known side effects.

Since the appearance of the Executive Summary in 2007,⁴ all these concepts and details have simply been refined in successive annual updates. Figure 5.3–7 of the last update of 2010,⁷ which debuted in the 2007 version⁴ and is the most widely cited in the current literature, perfectly illustrates the aforementioned, recommending that the addition of inhaled glucocorticoids to the long-acting bronchodilators should be centered on those symptomatic patients starting from GOLD stage 3 (FEV₁ <50%) who have had exacerbations (e.g. 3 episodes in the last 3 years). It is worth mentioning, however, that a recent post-hoc analysis suggests raising the FEV₁ threshold to <60% (evidence B), as the therapeutic efficacy on lung function is also found in this new spirometric link.^{7,8} The recommendation of inhaled glucocorticoids combined with a long-acting beta agonist (evidence A), administered either together or separately, is based in the fact that they are significantly effective for improving lung function and state of health and in reducing exacerbations. And if this is combined with a long-acting anticholinergic (tiotropium), there may be complementary therapeutic benefits.⁹ In summary, the GOLD Initiative has always recommended the use of inhaled glucocorticoids in patients with severe and very severe COPD, depending on their clinical and spirometric state.

In my opinion, there is a certain somewhat-hypertrophied criticism when the GOLD Initiative brazenly and almost exclusively insists on the spirometric criteria and ignores other essential aspects of the disease such as its symptoms, health-related quality of life and exacerbations. This criticism is not acceptable as, according to what has been previously commented, it has not been, nor is it, this way. The current alternative, based on clinical severity (including exacerbations) and spirometric severity by the identification of potential phenotypes,^{10,11} seems to me to be an arduous, if not questionable, task. It should be remembered that for more than 25 years the medical community pivoted around two universal COPD phenotypes, type A (pulmonary emphysema) and type B (chronic bronchitis), product of the subjacent clinical heterogeneity, a categorization that is now obsolete due to its lack of clinical utility. It is also worth mentioning the recent description of the phenotype of the COPD patient with “frequent exacerbations”,¹² which has confirmed and refined findings previously indicated in prior studies like EFRAM (Spanish acronym for *study of the potentially modifiable risk factors of COPD exacerbations*),¹³ stating that it is not going to be easy to explore where a change should be directed in the current therapeutic strategy in so-called “frequent exacerbation” patients.¹⁴ With or without the help of phenotypes, the indication for inhaled glucocorticoids combined with a long-acting beta agonist in stable COPD does not seem to be going to change in the next few years regarding the current recommendation. Spirometric severity, symptoms (especially dyspnea) and history of exacerbations in COPD patients should continue to be the three fundamental pillars to support said strategy focused on patients with GOLD

stages 3 and 4. We still must wait for a while in order to calibrate the practical results of the use of the new phosphodiesterase-4 inhibitor, roflumilast, the first oral anti-inflammatory medication designed for stable COPD that has been recently incorporated.⁷ Its recommendation, as a complementary medication to beta agonist bronchodilators and inhaled glucocorticosteroids in patients with GOLD stages 3 and 4 with abundant expectoration,¹⁵ may be of great therapeutic interest to optimize the already commented bronchodilator-glucocorticosteroid combination.

In any case, it should be said aloud that things have not been done badly until now and, in this regard, that positive progress has been made in the right direction. One example of this is the study by Almagro et al.¹⁶ done in Spain. It demonstrates a significant improvement of 10% in the 3-year survival in patients hospitalized for COPD exacerbation during the 2002–2003 period when compared with the 1996–1997 period. This improvement has been explained by the progressive use and better understanding of all types of long-acting bronchodilators and, of course, of the inhaled glucocorticosteroids in these patients. This is excellent new, additional scientific evidence to take into account in directing the therapeutic future of patients with stable COPD.

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