



Editorial

Arguments in Favor of Inhaled Corticosteroids in COPD by Phenotype Instead of by Severity[☆]

Corticoides inhalados en la EPOC por fenotipo en lugar de por gravedad. Argumentos a favor

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ARTICLE INFO

Article history:

Received 7 January 2011

Accepted 12 January 2011

The usual approach to the treatment of chronic diseases is to increase the dose of medication or to add new drugs to the treatment as the symptoms become more severe. COPD is no exception, and the guidelines recommend introducing inhaled corticosteroids (ICS) when the FEV₁ drops below 50% of the predicted value.^{1,2} Obviously, the guidelines are based on the best evidence available and studies such as ISOLDE showed that fluticasone (FLU) 500 mg/12 h was capable of significantly reducing exacerbations in patients with FEV₁ <50%.³ Concerning these results, two observations should be made: (a) the exacerbations were also reduced in patients with FEV₁ >50%; in fact, the reduction was even greater, from 0.92 episodes/year in the placebo group to 0.67 with FLU, a reduction of 27%, not significant due to the low number of episodes and lack of sufficient statistical power, compared with a reduction of 16% in patients with FEV₁ <50% (from 1.75 episodes/year with placebo to 1.47 with FLU; *p* = .022, thanks to a greater number of episodes)³; (b) these numbers are an average result for the whole population, and we do not know whether there are patients in whom the reduction is very important and others in whom it is inexistent, a fact which is crucial in making therapeutic decisions with each specific patient in our daily practice.

The identification of responders is key in the case of the use of ICS in COPD. The resistance of the neutrophilic inflammation typical of COPD to the action of the corticosteroids is perfectly described.⁴ In addition, the inactivation of histone deacetylase in COPD is an additional mechanism of resistance to ICS.⁵ However, COPD is a sort of ragbag where anything goes,⁶ and the undefined definition of a FEV₁/FVC <0.7 opens the door to diagnosing as COPD a multitude of diverse patients, some of whom may have a different inflam-

matory pattern and respond to ICS.⁷ From the beginning of the 1990s, we know that the patients with COPD that present a positive bronchodilator test (BT) respond with greater frequency and intensity to ICS.^{8,9} Later studies have confirmed this observation^{10,11} and have extended it to the ICS used in combination with a long-acting beta-adrenergic (LABA).¹² The link that joins BT and the response to ICS are seen in the patterns of inflammation associated with the bronchodilator response. The patients with positive BT have a greater bronchial eosinophilic inflammation compared with the non-reversible ones¹³ and the eosinophils are extraordinarily sensitive to the action of the corticosteroids. Along the same lines, Leuppi et al.¹⁴ demonstrated that among their patients with COPD only those with bronchial hyperresponse identified by a positive provocation test with mannitol responded to 3 months of treatment with ICS. Another marker of the eosinophilic inflammation in COPD, such as the fraction of exhaled nitric oxide (FeNO), has been shown to be related with the response to ICS, in lung function as well as in effort capacity and in respiratory symptoms.^{15–17} It has even been demonstrated that a normal concentration of FeNO in COPD has a negative predictive value for clinical response to ICS of 87%.¹⁶ Given these results, it is inevitable to ask: how is it possible to prescribe ICS in high doses indefinitely in COPD patients, most of whom are seniors, many polymedicated and some even fragile, without previously confirming or verifying if they are going to respond to treatment? Should not we try to ensure in every way possible that our patient is going to obtain some benefit from ICS before prescribing them just because he/she has an FEV₁ <50%? Or maybe, as they are incorporated in a combination, we do so “just in case”? It is not necessary to remind oneself that they are not innocuous¹⁸ and that they contribute to high COPD treatment costs.¹⁹ We have more and more simple strategies for identifying the responders to ICS: previous history of asthma, atopy, positive BT, bronchial hyperresponse, high FeNO, eosinophilia in sputum. Probably none is 100% sensitive or specific, but the integration of either all of them or several of them in the clinical judgment would allow for a much better

[☆] Please cite this article as: Miravittles M. Corticoides inhalados en la EPOC por fenotipo en lugar de por gravedad. Argumentos a favor. Arch Bronconeumol. 2011;47:271–3.

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prescription of these drugs, which are an irreplaceable help in the treatment of those who are responsive or can be an enemy for those who are not.

At this point, we should be reminded of why BT has been reviled as a test with prognostic value in COPD. Most of the blames lies in the study published by Calverley et al.²⁰ with data from the screening of the ISOLDE study. The final conclusion, after the patients had undergone 3 BT over the course of 2 months, was that to classify the patients as positive or negative by BT was not reliable. But if we look at the design, we see three critical points: (a) the patients with a reversibility higher than 10% in the first BT were excluded, which implies that the most reversible patients were excluded, and therefore the results cannot be extrapolated to all COPD cases; (b) the 3 BT were done with different protocols, therefore it should not be so strange to find different results; and (c) the majority of the patients presented a reversibility close to the cut-point (+12%), therefore the variability of the measurement itself can mean that one day the test is positive (e.g. +12.2%) and the next it is negative (e.g. +11.8%), which in no way implies that the reversibility has changed clinically. What this study indicates is that we should not use a continuous variable (reversibility) as a categorical one (positive or negative). Instead, what is important is its magnitude. In fact, a recent study shows an excellent correlation between the response to BT and the increase in FEV₁ after 3 months of treatment with an ICS plus a LABA.²¹

How did we reach this situation? By false oversimplification. We have gone from the “blue bloater”, “pink puffer”, smoker’s bronchitis, asthmatic bronchitis, bronchiectasis in smokers, etc., to the unitarian concept of COPD as post-bronchodilator FEV₁/FVC <0.7 and we have adopted a treatment pattern that is the same for all based on the severity of the obstruction. Once again, it is a false oversimplification. In studying more than 5000 young adults for 10 years, De Marco et al.²² observed how the COPD developed by some young asthmatics was very different from the COPD developed by the non-asthmatics. The former had greater bronchial hyperresponse, greater concentrations of immunoglobulin E, greater frequency of positive BT and was associated with more allergic rhinitis and wheezing. It is what later was defined as the *overlap* syndrome between asthma and COPD^{7,23} in patients with post-bronchodilator FEV₁/FVC <0.7 and great variability in the obstruction of the air flow. It may be these (and perhaps only these) patients with COPD that should be treated with ICS, regardless of their degree of airflow obstruction and, as occurs in asthma, at the lowest effective dose possible. Some guidelines, such as the Canadian, already dare make such recommendations: “*If the asthma component is prominent, earlier introduction of ICS may be justified*”.²⁴ The concept of COPD as a disease resistant to ICS has led us to the erroneous concept of using the greatest possible dose. Corticosteroid resistance is not a problem of dose but of type of inflammation and, in fact, there are no studies demonstrating better clinical results with greater doses of ICS. The results of the studies carried out in the USA with FLU at 250 mg/12 h (which is the dosage accepted by the Food and Drug Administration for the treatment of COPD in the US)²⁵ are perfectly equivalent to the results of European studies with FLU at a dosage of 500 mg/12 h.²⁶ Furthermore, a recent systematic review found no relationship between the modest clinical benefits of ICS in COPD (as defined by the authors) and the severity of the obstruction.²⁷

Therefore, it is time to change the paradigm from the current “ICS at high doses for all COPD patients with FEV₁ <50% and more than one exacerbation a year” to the new “ICS at the minimal effective dose for all those patients with COPD who are responsive (*overlap*), whatever their FEV₁”. This means going from an indication by severity to an indication by phenotype.^{28–31} It is clear that this will require an additional effort by the specialist, but it will undoubtedly be worth it for our patients.

Last of all, for those fans of medicine based on evidence, I will remind you of the results of a randomized clinical assay that compared the results of the treatment with ICS in patients with COPD, according to whether it was required in accordance with the guidelines (those of the British Thoracic Society, basically the same as GOLD) or in accordance with the eosinophilic inflammatory profile in induced sputum (only administering ICS to those patients with high concentration of eosinophils). At the end of a year of follow-up, the patients treated with ICS depending on their concentration of eosinophils had significantly less exacerbations and hospitalizations than those treated strictly according to the guidelines.³² The data is evident: treatment by phenotype wins by a mile over treatment by severity. The only option we have left is to change the guidelines. Let us hope that the light of reason and scientific evidence guides our leaders as they compose the new COPD treatment guidelines.

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