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Editorial

Treatment Strategies in Chronic Obstructive Pulmonary Disease: A Proposal for Standardisation

Estrategias de tratamiento en la enfermedad pulmonar obstructiva crónica: una propuesta de sistematización

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Introduction

Despite the significant advances made in recent decades, chronic obstructive pulmonary disease (COPD) is still a major health problem. Since 1977, when Fletcher and Peto discovered FEV_1 curves in patients who smoked,[1] COPD has invariably been associated with this functional disorder, causing FEV_1 to become established as the main parameter for the diagnosis, treatment and follow-up of patients. Thus, current national and international guidelines use this functional parameter as the basis for establishing severity and treatment.[2,3]

However, although FEV_1 is a good prognostic marker,[4] treatment strategies based exclusively on FEV_1 have not managed to cover all the clinical manifestations of the disease, as there are other clinical and prognostic variables that are expressed independently of FEV_1 and could be treatment objectives. For this reason, in recent years the need has become clear to consider other clinical aspects as aims within the therapeutic strategy for COPD.[5] These variables include the degree of dyspnea, the number of exacerbations, exercise capacity, or body composition, among others. In the last few years several indices and multidimensional questionnaires with implications for prognosis have been developed which take some of these variables into consideration.[6-9] However, for the time being these initiatives have not resulted in definite treatment proposals for everyday clinical practice. It is necessary, therefore, to establish a treatment strategy that takes into consideration some of the disease's other clinical variables that help to outline the maintenance treatment.

Below, we will review the available evidence in order to develop a proposal for a strategy to enable treatment standardization for this disease. Some of the declarations our review will be based on are supported by evidence provided by large clinical trials. We will also make use of less significant, but valid, clinical studies. Lastly, during this process we will also come across grey areas for which very little information is available. In these cases, we will use our clinical experience to make a decision about treatment. Ultimately, we will have a treatment model that, while having some controversial aspects, will serve as a framework for discussion enabling the debate about standardizing stable COPD treatment to continue.

Selecting Variables

The first step is selecting the variables to be included in the treatment model. Many clinical, functional, and morphological variables could be taken into account when establishing a treatment strategy. However, as we want to obtain a model that is easy to apply in daily clinical practice, it seems reasonable to include a limited number of variables, with a clinical profile.

Current guidelines make the assumption that as FEV_1 gets worse, so do the chronic respiratory symptoms.[2,3] Although this is generally true, we understand that this is not always the case with specific patients, as FEV_1 correlates poorly with chronic respiratory symptoms such as dyspnea.[10] Therefore, in our opinion, an assessment of clinical data from stable patients should be added to FEV_1 as an independent variable to be considered in a treatment model. As such, COPD is known to produce a wide range of symptoms, including dyspnea, fatigue, limited exercise capacity, coughing, and expectoration. Each of these symptoms could be used as a guideline for establishing a treatment strategy. Furthermore, other more complex concepts, such as quality of life or multidimensional scales, could also be selected within this treatment axis. In our case, we choose dyspnea, as it is one of the most common and incapacitating symptoms. Characterizing COPD patients by dyspnea has been shown to be a better predictor of 5-year survival than FEV_1.[11] In our model, we classify dyspnea using a modified version of the Medical Research Council's scale,[12] which uses a 5-point grading system from 0 to 4.

Exacerbations also have clinical and prognostic relevance in COPD. Although their definition is a topic of debate,[13] patients suffering from them frequently, have shown that their FEV_1 decreases much more significantly.[14] Furthermore, the number of exacerbations has an impact on survival, especially on those requiring hospitalisation,[15]

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and it has repercussions on numerous clinical variables.[16] Therefore, in view of the foregoing, FEV_1, dyspnea, and the number of exacerbations are the 3 variables we selected to construct our treatment model.

Treating Each Component Separately

The next step in the model construction is to establish a strategy for treating each of the selected components separately. In this respect, the guidelines agree on the use of bronchodilators for the base treatment of stable COPD.[2,3] Therefore, treatment usually begins with these drugs. On the other hand, when the disease is very advanced, the standard treatment used is triple therapy, which involves the combined use of a long-acting muscarinic antagonist (LAMA), a long-acting inhaled beta2-agonist (LABA), and an inhaled corticosteroid (IC).[2,3] The problem lies in the intermediate stages, as the guidelines are not clear as to whether it is more recommendable to add a long-acting bronchodilator or an early IC. Below, we will analyze each of these treatment axes independently to try to resolve this dilemma.

Pulmonary Function

From a functional perspective, there are clinical trials that provide valid information about both possibilities. On the one hand, we know that adding bronchodilator treatment twice daily has an additional functional effect.[17] On the other hand, TORCH study results show that introducing an IC has a positive effect on prognosis, even in the early stages of the disease with FEV_1>50%.[18,19] The only study comparing both strategies compared LABA+LAMA with LABA+CI and reported that the combination of bronchodilators showed a greater functional benefit.[20] These data suggest that the best choice is to begin with 2 bronchodilators before introducing the IC.

However, the best treatment strategy based on pulmonary function is probably not the same for all patients. In this respect, more and more data is becoming available about the variability of functional limitations in COPD. The variability of the obstruction can be expressed with 2 different, yet complimentary, concepts: bronchodilator reversibility and bronchial hyper-responsiveness. Regarding bronchial reversibility, it is now accepted that COPD patients can improve in bronchodilator testing and that these improvements can be significant.[21] Furthermore, recent clinical studies show that bronchodilator patients respond better to treatment with LABA+IC.[22] However, some authors suggest that bronchial reversibility does not appear to be constant over time and think that dividing patients according to this characteristic may be a mistake,[23,24] meaning that it is a controversial issue.

On the other hand, bronchial hyper-responsiveness seems to be relevant in COPD, with importance for the prognosis.[25] Recently, in a study of 114 COPD patients with a mean FEV_1 of 61% with no prior treatment with an IC, Lapperre et al[26] observed that those who began treatment with an IC made significant improvements in the bronchial provocation test with methacholine. Furthermore, the authors detected changes in cellularity in these patients, and so may have identified patients with a phenotype with the clinical characteristic of greater variability, and which may respond better to IC.

Therefore, in recent years there has been growing evidence that COPD patients may show variations in respiratory function, that this variability is important in the disease's clinical presentation, and that these patients' response to treatment may be different, thus recommending early ICs may be better in these cases. To this effect, some authors suggest that COPD patients and clinical features of asthma could respond well to ICs.[27] Although this idea is still controversial, if it were confirmed, doctors could opt to begin treatment depending on whether or not there were clinical manifestations of this variability, such as changes in air flow. A strategy could be created to standardize treatment in accordance with the FEV_1, summarized in Table 1.

Dyspnea

Treatment of dyspnea is the second axis of our model. Differentiating between the use of 2 bronchodilators and 1 with an IC is the most controversial issue with regard to dyspnea treatment. At present, many clinical trials are studying the role of the combination of 2 long-lasting bronchodilators of a different class (LABA+LAMA). The results of these trials are fairly consistent. The combined use of these drugs leads to improvements in function, with less need for rescue medication, and higher scores in questionnaires about symptoms and quality of life.[17,28] On the other hand, trials with LABA+IC produce statistically significant improvements in dyspnea but, at times, they do not reach clinical significance. Lastly, the only trial comparing these two treatment strategies was performed by Rabe et al,[20] who found that a combination of bronchodilators had a greater effect on lung function than LABA+IC. Therefore, a possible strategy to treat dyspnea, could be to add a second bronchodilator before the IC.

However, it is important to remember that pulmonary rehabilitation has consistently shown significant improvements in dyspnea and chronic symptoms.[29] Therefore, centers with pulmonary rehabilitation programmes should include them at an early stage of treatment algorithms.

Exacerbations

Treatment with a LABA, LAMA or IC also reduces the number of exacerbations, meaning that it is difficult to set out a specific treatment strategy with this aim. In this respect, it is necessary to remember two important studies. The first is the OPTIMAL study,[30] performed to assess the effect on exacerbations when adding an IC in patients under treatment with a LABA or LAMA. The study was negative, failing to show that any of the lines of treatment were better than another with regards the number of exacerbations. However, the authors observed that adding an IC did lead to a significant reduction in hospitalization. These results suggest that is important to assess the number of exacerbations and their severity when choosing treatment. Secondly, an aggregate analysis of clinical trials showed that adding an IC reduces the number of exacerbations compared with bronchodilators.[31] Therefore, it seems that ICs play a particularly important role in patients with numerous or severe exacerbations, especially those requiring hospitalization, and that they should be used earlier in these cases.

Standardizing Treatment

Once we have therapeutic strategies for each of our 3 axes, the next step is to combine them into a single treatment model. One possible way of considering the 3 axes would be to represent them in the shape of a dartboard, joining the points to form a treatment target for COPD, as shown in Figure 1. We therefore establish the pharmacological treatment in three steps on these axes: 1) treatment

Table 1
Proposal for standardizing treatment of stable chronic obstructive pulmonary disease, in accordance with the component of lung function

FEV_1	Clinical variability	Initial treatment
>50%	Absent	1 inhaled bronchodilator
	Present	Bronchodilator+IC
<50%	Absent	2 inhaled bronchodilators
	Present	Inhaled "triple therapy"

Abbreviation: IC, inhaled corticosteroid.

with an LABD; 2) treatment with 2 LABDs or with an LABD and an IC depending on whether the clinical variability is present or not or on the severity and frequency of exacerbations; and 3) triple therapy, combining LABA+LABA+CI. In this model, the treatment strategy depends on which axis has the worst symptoms. For example, in a patient with a FEV_1 of 62%, with grade 1 dyspnea on the Medical Research Council scale and more than 2 exacerbations, the treatment would be guided by the exacerbations, the patient's main problem. In short, it consists of finding out which of the three (pulmonary function, chronic symptoms, or exacerbations) is the patient's main problem and using the treatment strategy on that axis.

This can also be represented in a table of treatments (Table 2), where, as chronic symptoms increase so would bronchodilator treatment, while a greater number or severity of exacerbations would involve increasing anti-inflammatory treatment.

This model has some limitations. Firstly, we must remember that many of the exacerbations suffered by COPD patients are not recorded[32] and that they affect their quality of life.[33] Therefore, it is important to collect information about COPD patients' exacerbations in the most reliable way with a view to establishing a treatment strategy, and if this is not possible, the model should be limited to exacerbations that are objectively recorded by a healthcare centre.

Secondly, as mentioned above, the model for bronchial reversibility is controversial and requires follow-up studies that provide information about its long-term importance, and clinical trials that look deeper into these patients' response to different treatments. Furthermore, a precise definition of the concept of clinical variability would be needed and its effect on prognosis and how those patients' respond to treatment should be studied.

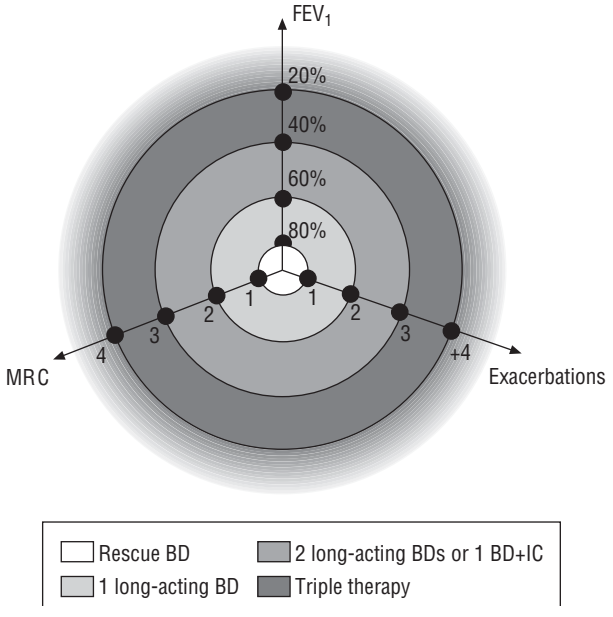

Figure 1. Three-dimensional treatment strategy. IC indicates inhaled corticosteroid.

Another controversial aspect is the definition of "frequent exacerbations", with regards the number of exacerbations the patient must suffer for them to be considered frequent. In Table 2, the limit has arbitrarily been placed at 1, but some authors consider the limit to be 2 exacerbations per year, and the limits depend on the different guidelines.[2,3,15] If we wanted to select patients with more exacerbations, this limit would have to be increased.

Lastly, it is necessary for future clinical trials to make progress in the efficacy and safety of combinations of bronchodilators compared with combinations of a bronchodilator and an IC, so that these options can be situated within a treatment strategy in a suitable way.

Conclusion

It has become clear in recent years that treatment strategies guided exclusively by FEV_1 have not managed to include the treatment of all the clinical manifestations of COPD. A change is necessary in the treatment strategy for the disease, progressing from one-dimensional models involving FEV_1 to three-dimensional ones like the one presented here, or even multidimensional ones. These models would help doctors establish a treatment plan in line with the real clinical situation of each case. The model presented here does include some controversial aspects, but we believe it could be a starting point for establishing a forum for debate which would enable a treatment strategy appropriate for COPD patients to be established in the future.

Conflict of Interest

The author has received fees for giving conferences, scientific consultancy, participating in clinical trials or writing articles for the following (in alphabetical order): Almirall, AstraZeneca, Bayer, Boehringer Ingelheim, Cantabria Pharma, Chiesi, Esteve, GlaxoSmithKline, MSD, Novartis and Pfizer.

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Table 2
Three-dimensional treatment strategy

	FEV_1>50%		FEV_1<50%	
	MRC 0-1	MRC>1	*MRC 0-1*	MRC>1
Exacerbations 0-1	LABD	2 LABD 1 BD+rehabilitation	2 LABD	2 LABD-rehabilitation
Exacerbations >1	LABD+IC	Triple, rehabilitation	Triple	Triple, rehabilitation

Abbreviations: IC, inhaled corticosteroid; LABD, long-acting bronchodilator; MRC, Medical Research Council; Triple, triple therapy.

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