EDITORIAL

Combination therapy for chronic obstructive pulmonary disease: one size fits all?

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Without hesitation I would acknowledge that combination products with fixed doses of long-acting β -adrenoceptor agonists and inhaled corticosteroids are an established therapeutic option for asthma in patients with moderate and severe disease. These drugs have changed conceptual views of asthma treatment and may have simplified asthma management, which is probably one of their greatest merits! There is a reasonable scientific basis for the use of combination therapy [1] that convinced us that the fixed combination of bronchodilators with inhaled steroids is the treatment of choice, at least for patients that are not sufficiently controlled with a short-acting β -agonist and an inhaled steroid. I still find it puzzling that the same doses of drugs given in one inhaler should have a greater effect in these patients compared to the single components (at least in the first weeks of treatment), but that's the data and all published studies irrespective of sponsorship come to the same conclusion. As this is the evidence, I am happy to adopt this strategy.

But chronic obstructive pulmonary disease (COPD)? We have all witnessed the heated discussions around inhaled steroids in COPD and have seen and read the data that confirm that asthma and COPD are completely different diseases, clinically and biologically. I can see the role of long-acting bronchodilators for the treatment of COPD, an issue that is already addressed in the updated Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines [2], but the use of inhaled steroids and combination therapy as in asthma? Is this a "one size fits all" strategy that is driven by commercial interests? And, were we all wrong, does this mean we no longer need to differentiate between asthma and COPD since the treatment will be the same in the end?

At this point the available evidence should probably be considered. In this issue of the *European Respiratory Journal*, P. Calverley and co-authors [3] (yes, the TRISTAN P. Calverley [4]) present the second large clinical study of 2003 that demonstrates that maintenance treatment with a fixed dose of an inhaled steroid (budesonide) and long-acting β -agonists (formoterol) in COPD improves lung function, quality of life and delays the time to first exacerbation and that this effect is more pronounced with the combination therapy than in either component alone. One-thousand and twenty-two COPD patients (with 629 or 62% completing the study) with a mean forced expiratory volume in one second (FEV₁) of 36% predicted were included in this multicentre trial and were randomised to receive either budesonide or formoterol or the combination of both or placebo, with terbutaline as rescue medication. Randomisation followed a run-in period of 2 weeks during which patients were treated with 30 mg oral prednisolone and formoterol *b.i.d.*, and terbutaline as rescue medication. The primary outcomes of

this trial were the time to first exacerbation and change in FEV₁. The authors also recorded data on peak expiratory flow, health-related quality of life, symptoms, use of reliever medication and adverse events.

Is there anything wrong with this study? No, otherwise you would not find it in a high-quality Journal such as the *ERJ*. It is potentially an important clinical study but there are some issues that need to be highlighted to put the data into perspective. The present study is the third to assess the effect of combination therapy in COPD. However, the design differs to the other two [4, 5] as the run-in period comprises a treatment optimisation with oral steroids, leading to a significant improvement of patients with an FEV₁ increase of 210 mL and a health status improvement of 4.5 units, exceeding the magic 4.0 line by 0.5 points. It is therefore correct, as stated by the authors, that in this study, combination therapy maintains the effect of treatment optimisation with reference to patients with these characteristics. However, it is surprising that the deterioration of patients occurs so rapidly (within days) in the other treatment groups, including those that were treated with budesonide only.

Compared to the other two available studies [4, 5], the long-acting β -adrenoceptor agonist alone did not affect the time to first exacerbation compared to placebo while the combination therapy clearly did [3]. The authors correctly defined an exacerbation as an episode requiring oral steroids and/or antibiotic treatment and analysed those episodes requiring steroids separately. The data seem to indicate that patients experiencing more severe exacerbations benefit the most from combination therapy and confirm, to some extent, the findings from the TRISTAN trial by the same author [4]. If the definition of a (mild) exacerbation for clinical trials also includes aggravation of symptoms, such as in the paper by SZAFRANSKI *et al.* [5], the relative effect of a long-acting bronchodilator might be more pronounced. This is also evident in the present study in which formoterol alone had a significant effect on symptoms such as shortness of breath, chest tightness and night-time awakenings. This clearly highlights the importance of definitions of exacerbations for clinical trials and calls for studies comparing the effect of maximal bronchodilation with, for example, the combination of long-acting β -adrenoceptor agonists with long-acting anticholinergics in COPD with mild and severe exacerbations as an outcome.

Does this paper tell us why combination therapy has improved efficacy in this group of COPD patients? No (see Discussion in [3]), but this paper does provide evidence that in advanced disease, after a steroid trial with measurable lung function and symptomatic improvement, combination therapy is an effective treatment option. This might also imply that physicians who are not aware of the individual risk of exacerbations in a given patient with an FEV₁ <50% pred should consider an oral steroid course to help them in their decision of how to proceed with maintenance treatment.

Does this study in patients with COPD (and the other

available evidence) suggest that combination therapy with inhaled corticosteroids and long-acting β -adrenoceptor agonists is a "one size fits all" option for all patients with a low FEV₁, making the differential diagnosis between asthma and COPD redundant? This would not only result in the extinction of pulmonologists dealing with obstructive lung diseases but it would also be wrong! The role of steroids in the treatment of patients with asthma [6] is fundamentally different compared to COPD [7–11], since the perceptions of symptoms in asthma and the evidence for early intervention probably favour the use of these drugs in combination with bronchodilators in the future in even earlier stages of the disease than currently recommended. In contrast, asymptomatic COPD patients should not be treated with drugs, and this alone, amongst other considerations, clearly calls for a differentiation of these two diseases that are fundamentally different in the vast majority of patients. In advanced disease states the treatment algorithms admittedly become more similar and the present study provides additional evidence for the use of combination therapy in patients with COPD. However, all published studies, including the present paper in the *ERJ*, support the current GOLD guidelines that combination therapy with inhaled steroids and long-acting β -adrenoceptor agonists should be reserved for COPD patients with advanced disease (FEV₁ <50% pred) and a history of frequent (more than one) "real" exacerbations per year [12]. For the remainder, further studies on the role of maximal bronchodilator therapy are urgently needed.

For the clinical reader of the *European Respiratory Journal*, the present paper might provide a practical approach to new patients in which the exacerbation history is not known. A steroid optimisation period for 2 weeks might not only help to differentiate between asthma and chronic obstructive pulmonary disease, it will probably help to identify chronic obstructive pulmonary disease patients who will undoubtedly benefit from combination therapy.

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