

What is the best pharmacological treatment to prevent exacerbation of chronic obstructive pulmonary disease?

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Chronic obstructive pulmonary disease (COPD) is and will continue to be an important cause of morbidity and mortality in the world. The progressive nature of the disease is punctuated in many patients by episodes of exacerbations characterized by worsening dyspnea, cough and sputum that require change in therapy. These episodes are important because they may result not only in symptomatic compromise but also in respiratory failure, which may lead to hospitalizations and death [1]. Exacerbations impact on health status [2], functional capacity [3] lead to more rapid decline in lung function [3,4] and account for a large portion of health care costs of patients with COPD [1]. Thus, it has become clear that prevention of exacerbation is an important goal in the comprehensive care of patients with COPD.

The results of several important trials designed to evaluate the effectiveness of currently available medications on exacerbations provide clinicians with evidence that pharmacotherapy is effective. However, the choice of the best therapy remains debatable. Should the first choice be monotherapy with one of the long acting agents such as tiotropium, salmeterol or formoterol? Or is it better to provide therapy with a combination of inhaled corticosteroids (ICS) and a long acting β -agonist (LABA)?

In a large 6 months trial, tiotropium reduced exacerbations by close to 20% when compared with usual care including short acting beta-agonists and anticholinergics [5] supporting that long acting agents are superior than short acting ones. Similarly, a recent meta-analysis pooling results from seven randomized trials [6] support the concept that the combination of ICS/LABA is superior in preventing exacerbations than ICS alone by approximately 9%. In addition, there appeared to be a reduction in mortality in favor of the combination over ICS alone. The same authors performed a meta-analysis com-

paring the combinations of ICS/LABA with LABA alone [7]. In the 10 studies reviewed, which included over 7500 patients, the ICS/LABA combination was superior than LABA alone in preventing exacerbation reducing them by approximately 20%. The combination was also associated with better scores in the health status questionnaires and in degree of airflow obstruction. In contrast, there was no difference in hospitalizations and in mortality. This benefit has to be considered against the increased incidence of pneumonia first reported in the TORCH trial [8] and confirmed in the meta-analysis.

But, could it be that tiotropium is as good ICS/LABA in the prevention of exacerbations? Although the final answer is still to be determined, the question is beginning to be addressed by two recent studies. In the first one by Aaron and co-workers [9] randomized over 400 patients with symptomatic COPD into three groups; the first group to tiotropium combined with placebo, the second group to tiotropium combined with salmeterol and the third group to tiotropium and the combination of salmeterol and fluticasone or triple therapy. The exacerbation rate (primary outcome) was similar among the groups. However, the number of hospitalizations, health related quality of life and lung function (all secondary outcomes) was significantly better in the group receiving tiotropium plus salmeterol and fluticasone compared with tiotropium plus placebo and tiotropium plus salmeterol. This suggests that tiotropium alone is as good as ICS/LABA combined or LABA alone in preventing exacerbation. However, the study was relatively small and underpowered to clarify the effects on the secondary outcomes. The most recent of the studies is the Investigating New Standards for Prophylaxis in Reducing Exacerbations or INSPIRE trial [10]. This prospective trial randomized of 1300 patients in 22 countries who had severe and very severe COPD ($FEV_1 < 50\%$ predicted) to receive tiotropium 18 micrograms or the fluticasone propionate/salmeterol (FP/S [500/50]) combination and followed the patients over two years. The utilization of health care resources (episodes requiring antibiotics and/or systemic corticosteroids or hospitalizations) was the same in both groups. There was more use of systemic corticosteroids during the exacerbations in patients receiving tiotropium whereas there was more use of antibiotics in the group of patients who exacerbated while receiving FP/S. There were more patients

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that withdrew from the study in the tiotropium arm and patients in this group had a significantly higher risk of death (6% vs. 3%) over the two years than the patients randomized to FP/S. There was a higher incidence of pneumonia in the FP/S group.

Taken together, all of the studies indicate that tiotropium and the combination of FP/S are equally effective in preventing exacerbations and should be recommended for the prevention of exacerbations over short acting bronchodilators, ICS or LABA as single agents. Although other combinations of ICS and LABA such as budesonide and formoterol or formoterol alone could have similar effects, as supported by limited size studies, more research with these and similar compounds are needed to extend the recommendations to those agents. The data from INSPIRE on mortality also supports

the findings first reported in TORCH, that the combination of ICS/LABA may actually improve survival and is indicated in patients with severe and very severe COPD, specially if they have repeated exacerbations. We eagerly await the results of the UPLIFT 4 year trial that is designed to evaluate the effectiveness of tiotropium in slowing lung function in patients with moderate to very severe COPD compared with usual care [11]. In this trial, exacerbation rate and mortality are important secondary endpoints that should help clarify the impact of tiotropium on the course of COPD. Finally, the current data supports the use of triple combination (tiotropium, ICS/LABA) as possible therapy to treat the more severe patients.

The last few years have seen significant advances in our understanding of COPD exacerbation and its treatment. We still have a lot to learn. We need better definitions to classify

From the Editor

Synopsis: Nannini LJ, Cates CJ, Lasserson TJ, et al. Combined corticosteroid and long-acting beta-agonist in one inhaler versus inhaled steroids for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev.* 2007; 4: CD006826.

In this systematic review with metaanalysis of 7 randomized controlled trials including 5708 patients with moderate or severe chronic obstructive pulmonary disease (COPD) without exacerbation within the last month, the authors observed that chronic (24–156 weeks) treatment with corticosteroid together with long acting beta-agonist (in one inhaler), in comparison with corticosteroid alone, reduces the rate of COPD exacerbations (rate ratio 0.91), reduces risk of death (OR 0.77) and improves the quality of life of the patients, without increase in the risk of pneumonia (OR 1.13).

Prepared by Małgorzata Bała, MD, PhD

Synopsis: Nannini LJ, Cates CJ, Lasserson TJ, et al. Combined corticosteroid and long-acting beta-agonist in one inhaler versus long-acting beta-agonists for chronic obstructive pulmonary disease (review). *Cochrane Database Syst Rev.* 2007; 4: CD006829.

In this systematic review with metaanalysis of 10 randomized controlled trials including 7598 patients with moderate or severe chronic obstructive pulmonary disease (COPD) without exacerbation within the last month, the authors observed that chronic (8–156 weeks) treatment with corticosteroid together with long acting beta-agonist (in one inhaler), in comparison with long acting beta-agonists alone, reduces the rate of COPD exacerbations (rate ratio 0.82) and improves the quality of life of the patients, but increases the risk of pneumonia (NNH 28). No difference in the risk of death was observed.

Prepared by Małgorzata Bała, MD, PhD

Synopsis: Wedzicha J, Calverley PM, Seemungal TA, et al. The prevention of chronic obstructive pulmonary disease exacerbations by salmeterol/fluticasone propionate or tiotropium bromide. The INSPIRE trial. *Am J Respir Crit Care Med.* 2007; 177: 19–26.

In this multicenter randomized controlled trial the effect of chronic 2-year inhaled combination of salmeterol/fluticasone propionate and tiotropium alone in 1332 patients with severe or very severe COPD. No differences in COPD exacerbation rate and lung function has been found between groups but patients receiving combined therapy has had lower death risk (NNT 33), better quality of life and higher risk of severe adverse events, including pneumonia (NNH 28). The high rate of people who dropped out of the study (40%) makes the interpretation of the results difficult.

Prepared by Wiktoria Leśniak, MD, PhD

their severity and cause (infectious or non-infectious) so that we can target therapies that may be tailored to the nature of the episode. For ethical reasons, we also need to move away from long term placebo controlled trials as we already have effective therapy to prevent these episodes. Finally, larger studies evaluating the effectiveness and safety of different combinations of therapeutic agents should help clarify the debate over the best agents to use in the prevention of COPD exacerbation.

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