Combining LABA and ICS in patients with severe COPD

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Does combination therapy with LABA and ICS provide clinical benefit in patients with severe COPD? Two recently published studies shed some extra light on this question.

Current management of COPD has been summarized in the latest 2006 update of clinical practice guidelines prepared by GOLD Initiative (fig.) [1].

It is worth remembering that LABD (long acting brochodilators) include here both long acting beta-agonists as well as long acting anticholinergic drugs. At the stage the guidelines do not make clear distinction or preference between those two classes of drugs.

The trial of Kardos [2], chronologically first, provided more support for a management strategy to include the combination of LABA and ICS in population similar to those patients included in the study. The overall impression from this study is that the patients had quite severe disease (FEV_1 <50% predicted and frequent (>2 per year) exacerbations), that it had adequate sample size and duration of follow up, that the results were both statistically and clinically important in term of exacerbations and also in terms of other outcomes (quality of life), suggesting an advantage of combination therapy over LABA alone.

The result of this study, which included almost 1000 patients followed on average for 44 weeks are, in general, consistent with just released data from yet larger and longer TORCH study [3]. In this experiment authors compared, over 3 year period, Fluticasone+Salmeterol combination *vs* individual components and placebo in 6112 COPD patients with average FEV_1 <45% predicted. Patients in each group could use short acting beta agonist salbutamol (ventolin). In TORCH [3] analysis the combination therapy was associated with reduced exacerbations rate versus not only placebo, but also against individual drugs, confirming the respective result from Kardos study [2]. Interestingly, in a very cautiously performed main mortality analysis the reduction in the risk of dying between combination group and placebo group was just above the level required to achieve statistical significance (absolute reduction 2.6%, relative 17.5%, HR 0.825, 95% CI 0.681–1.002, p = 0.052). The effect of combination was also suggestive but not conclusive on COPD-related mortality (HR 0.78, 95% CI 0.57–1.06, p = 0.1). The additional exploratory analysis of the data suggests to us and to the author of editorial in NEJM [4] that monotherapy with ICS should not be advocated for patients with COPD and that monotherapy with LABA appears to be safe (despite lack of direct comparison between those monotherapies). In addition, not only some of the analyses suggested that combination treatment was associated with lower mortality that mortality observed with individual component (in exploratory analysis difference statistically significant in case of ICS, smaller and not statistically different for LABA), but it was associated with improved COPD-specific quality of life and frequency of exacerbations (although not those exacerbations requiring hospitalizations). The increased pneumonia rate among patients receiving ICS (alone and in combination) tempers, however the extent of enthusiasm for dual therapy.

In summary, those two studies may not change current practice as interpreted from GOLD guidelines, but certainly will provide more confidence for those who use long-term bronchodilator and ICS combination, especially among patients with more severe disease.

As an added benefit TORCH study may also add extra insights to the debate surrounding recent reports and meta-analyses questioning the relative safety of long acting beta agonists when used in patients not taking inhaled corticosteroids [5]. Those reports based on meta-analyses coming from one group of authors and dealing with both asthma [6] and COPD [7] patients require further evaluation and extension to the population of COPD patients taking inhaled corticosteroids.

Results from these large trials have their limitation in managing individual patients with a disease as heterogeneous as COPD. The concept of "individualized therapy" is as or more relevant for COPD than for any other airway disease. It is hoped that in future interpretation of both research study data of this kind and its clinical application will be guided to a degree by information concerning level of inflammation present in the airways [8]. Methods of measuring airway inflammation, such as exhaled nitric oxide and quantitative sputum cell counts, have reached clinical practice, although sparsely. Of the two methods, sputum gives the most comprehensive information and is of most clinical value. Its use in practice is supported by recent publications and will appear in upgrades of the Global Initiative for Asthma and Canadian

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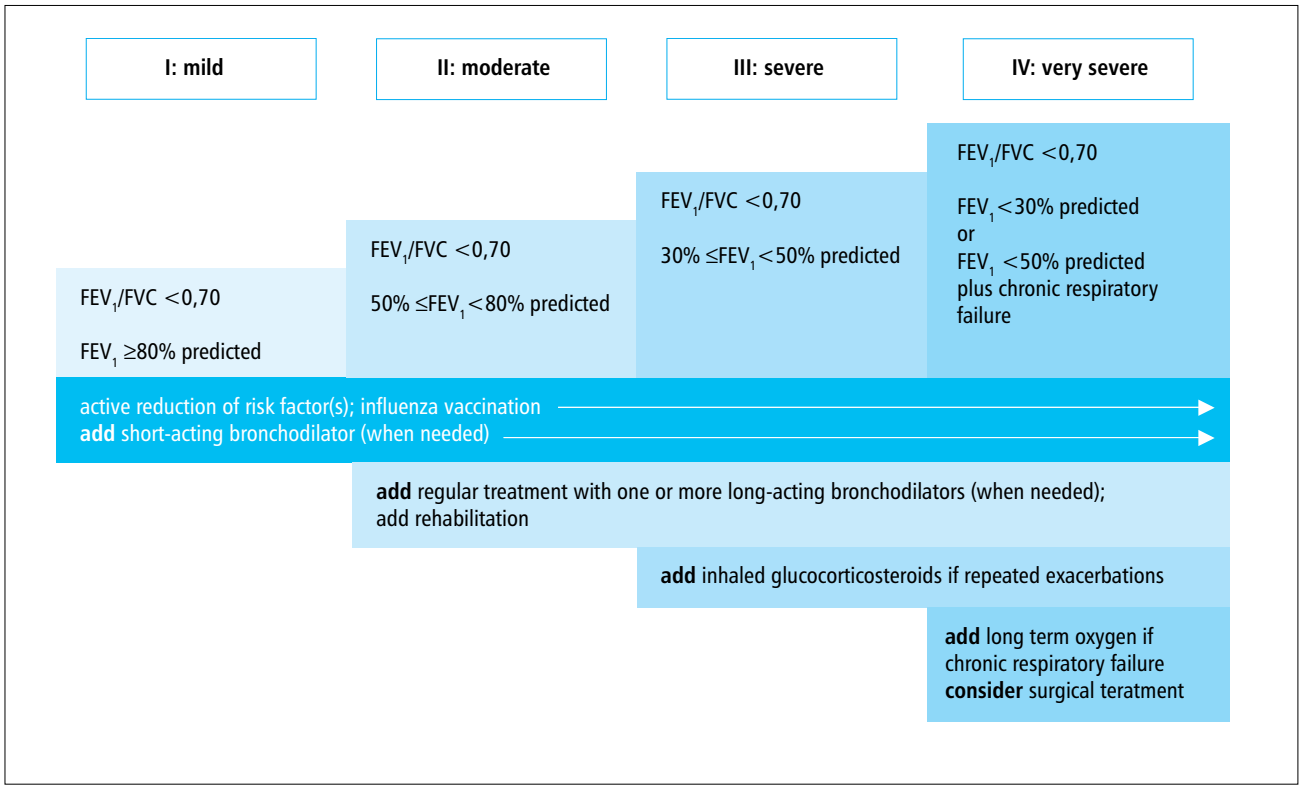

Figure. Clinical use of bronchodilator drugs

Asthma Treatment Guidelines. Such indices of inflammation may guide both diagnosing the type of disease or its exacerbation (for example, infective bronchitis versus worsening airflow obstruction versus non-infectious eosinophilic bronchitis etc). There is strong evidence that sputum eosinophilia (>3%) is a predictor of clinical improvement with oral and inhaled corticosteroid treatment not only in asthma but also in COPD [9,10]. Another study [11] did not observe any improvement in the percentage of sputum eosinophils although there was progressive improvement in FEV1 and quality of life. Leigh et al. [10] used, however, a higher dose of ICS (Pulmicort 800 micrograms twice daily, estimated to be approximately four times more potent than the dose of mometasone used by Brightling [11]), and demonstrated a reversal of the sputum eosinophilia and clinical improvement which was not improved further by 2 weeks of treatment with prednisone 30 mg daily. Hence moderate to severe COPD with sputum eosinophilia can be responsive to inhaled steroid but high doses may be required. The study also identified three other relevant issues concerning the investigation of the effect of inhaled corticosteroid, eosinophilic bronchitis and salbutamol FEV1 reversibility in COPD. First, if subjects were not divided into eosinophilic and noneosinophilic groups, no improvement following inhaled steroid treatment was demonstrated. This may be one reason why previous large multicentre studies of the effect of ICS in COPD, in which the type of airway inflammation was not considered, failed to show clear benefit. Secondly, eosinophilic bronchitis was not necessarily associated with the primary definition of asthma (i.e., with significant bronchodilator reversibility). Thirdly, such reversibility did not relate to steroid responsiveness. The frequent occurrence of viral and bacterial infective bronchitis as a cause of exacerbations in patients with asthma or COPD is becoming more evident. These tend to be noneosinophilic and to be associated with a mild to modest neutrophilia in viral infections and can be more intense in bacterial infections. As such, they should not benefit from corticosteroid treatment unless there is an associated eosinophilic bronchitis.

These considerations would suggest an approach that is different from that recommended by international guidelines in recommending inhaled steroids in patients with an eosinophilic bronchitis irrespective of the 'stage or severity' of the disease, not using corticosteroids when there is no eosinophilic bronchitis, and the addition of a long-acting bronchodilator in patients who have significant airflow obstruction or air trapping. This recommendation was recently proven in a randomized clinical trial that compared the British Thoracic Society COPD guideline strategy (BTS group) versus a strategy aimed at normalizing sputum eosinophil count in 82 patients with moderate airflow obstruction [12]. The frequency of severe exacerbations/patient/year was 0.5 in the BTS group and 0.2 in the sputum group (mean reduction 62%, $p = 0.037$). Most benefit was confined to patients with eosinophilic airway inflammation. There was no difference in the frequency of mild

and moderate exacerbations. The average daily dose of inhaled or oral corticosteroid during the trial did not differ between the groups. Out of 42 patients in the sputum group, 17 required regular oral corticosteroids to minimise eosinophilic airway inflammation. A management strategy that aims to minimise eosinophilic airway inflammation as well as symptoms is associated with a reduction in severe exacerbations of COPD.

At the end, let's recapitulate current main principles of COPD management. An attempt should be made to identify the components of the disease ie bronchitis and airflow obstruction to direct therapy against the abnormal component. Although work remains to be done on relative safety of different combinations of treatments, effective medications for COPD are available and all patients who are symptomatic merit a trial of drug(s) treatment. Therapy with currently available medications can reduce or abolish symptoms, increase exercise capacity, reduce the number and severity of exacerbations, improve health status and quality of life, and possibly prolong life. When different drug formulations are available the inhaled route is preferred as smaller doses of active treatment can be delivered directly without loss of efficacy and with fewer harmful effects. As significant numbers of patients cannot effectively coordinate their breathing with drug delivery using metered-dose inhaler, patients' education and alternative modes of delivery may be required (breath-activated inhaler, a dry powder inhaler (DPI) device or a spacer chamber). And let's not forget that clinicians should strive to identify, document, and treat every tobacco user at every visit.

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