Combination therapy in COPD: different response of COPD stages and predictivity of functional parameters

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Abstract. – Background: Inhaled corticosteroids reduce exacerbations in patients with chronic obstructive pulmonary disease (COPD) but they do not affect disease progression. FEV1, as single parameter, showed limits in describing the heterogeneity of COPD population. Combination therapy, with long-acting Beta2-agonist and corticosteroid, showed a more beneficial effect on lung function, exacerbations, and health status than single inhaled drug. The aim of this study was to assess, in stable COPD, which stage (mild, moderate, severe) shows the best response after 12 weeks inhaled treatment, and which starting functional parameters show a correlation with the response.

Methods: 170 stable COPD patients (38 mild, 66 moderate, 66 severe) were enrolled. Patients received salmeterol/fluticasone 50/500 µg Metered Dose Inhaler (MDI) bid for 12 weeks. Pulmonary function tests and clinical data were performed. Results were subdivided, on functional and clinical data, in “responders (R)” and “no-responders (NR)”.

Results: A FEV1 improvement (+12% and 200 ml) was achieved in 21 mild, 28 moderate and 17 severe COPD patients, respectively 55.3%, 45.9%, and 30.9% of each group. Statistical analysis of starting functional parameters showed a correlation with the therapeutical response for FEV1/FVC, MEF50 and DLCO/VA% (p < 0.05).

Conclusions: Salmeterol/fluticasone improves FEV1% in mild and moderate more than in severe COPD patients. The study confirmed the difference in response between early and advanced stage. Starting FEV1/FVC and MEF50 were significant predictors in mild and moderate stages, and starting DLCO/VA% resulted a significant predictor in moderate and severe stages.

Key Words: COPD, Salmeterol, Fluticasone propionate, Combination therapy.

Introduction

In chronic obstructive pulmonary disease (COPD) spirometry is an essential test in monitoring the evolution of the disease and the therapeutic response. FEV1 (forced expiratory volume in 1 second) is the functional parameter utilised in all the guidelines for its acceptable reproducibility and its easy carrying out1-3.

Many COPD classifications were succeeded because the difficulty to situate the characteristics of COPD patients only with FEV1 value, and the debate in understanding the disease management is still open4-5. In the last years the limit of FEV1 emerged in describing, as single parameter, the stages and the progression of the disease. This limit should be ascribed to the great heterogeneity of COPD population about the type of airways inflammation, the individual susceptibility in the progression of the disease and in therapeutic response, and particularly to a more careful immuno-pathophysiological knowledge and to appropriate management programme of the disease. Therefore the consideration of other spirometric parameters and clinical data proved to be indispensable for an accurate staging and control of the disease.

Many studies showed that combination therapy, containing long acting β2-agonist and corticosteroid, has more beneficial effects in the treatment of COPD on lung function, daily symptoms, exacerbations, and patients’ health status than single inhaled drug6-9.

GOLD guidelines for the management of COPD recommend a stepwise treatment approach. Bronchodilators are introduced early
for all patients with COPD, and inhaled corticosteroids are added only for those with severe disease (FEV₁ less than 50% of predicted), repeated exacerbations and a spirometric response to inhaled steroid. The ATS/ERS COPD guidelines 2004 support a significant additional effect on pulmonary function and a reduction in symptoms in those receiving combination therapy compared with its components, and a larger effect in terms of exacerbations and health status in patients with an FEV₁ < 50%.

Debated data on different therapeutic response, survival, quality of life, exacerbation, and rate of decline in FEV₁ suggest the need for further studies that are designed to evaluate subgroups of patients in whom inhaled therapy may induce the best effect.

Aim of this study was to assess in stable COPD which stage of the disease (mild, moderate, severe) shows the best therapeutic response after 12 weeks of inhaled combination therapy (salmeterol/fluticasone), and which starting functional parameters (at the enrolment) show a better correlation with the therapeutic response in the three different stages.

**Materials and Methods**

During two years (2001-2003) 170 patients suffering from COPD (38 mild, 66 moderate, and 66 severe – ERS classification) were enrolled in the study (Table I) in accordance with the following including criteria: stable COPD (no exacerbation), negative reversibility test with salbutamol (<12% of FEV₁), FEV₁/FVC < 70%, no-smoker patients (at least 3 months), absence of severe concomitant diseases (stroke, dementia, heart failure and arrhythmias, cancer, peptic ulcer), no treatments with oral corticosteroids, no patients with mechanical ventilation (Table II).

Patients received salmeterol/fluticasone propionate 50/500 µg MDI bid for 12 weeks.

**Table I.** Enrolled patients (170).

<table>
<thead>
<tr>
<th>Stage</th>
<th>Male</th>
<th>Female</th>
<th>Age (mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>19</td>
<td>19</td>
<td>64.5 ± 11.4</td>
</tr>
<tr>
<td>Moderate</td>
<td>42</td>
<td>24</td>
<td>67.9 ± 11.7</td>
</tr>
<tr>
<td>Severe</td>
<td>53</td>
<td>13</td>
<td>69.8 ± 8.5</td>
</tr>
</tbody>
</table>

Written informed consent was obtained by each subject. No placebo group was assented by Ethical Committee, basing on proved superiority of this therapy in many controlled studies and on the new ethical questions for its use.

At the enrolment, pulmonary function tests, including flow/volume spirometry, Slow Vital Capacity, N₂ Washout, and DLCO (CO Lung Diffusion), were performed, and clinical data (Oxygen saturation %, walking test, dyspnoea) were collected (Table III).

Pulmonary function tests were performed with a Cosmed Quark 4 spirometer (Cosmed, Pavona – Italy). Oxygen saturation % was collected with a pulse oximeter (Palmsat 2500, Nonin Medical Inc., Plymouth, Minnesota USA), a 6MWT (6-minute walk testing) was performed, and a VAS (visual analog scale) was used for dyspnoea. Patients with COPD exacerbation during the treatment were withdrawn.

At the end of the treatment were repeated the same functional tests and clinical data collection. Therapeutic effect was evaluated.
after 12 weeks, and the control of spirometric parameters was measured 24 hours after the suspension of inhaled therapy.

Therapeutic response was established on the improvement of functional lung parameters (FEV$_1$) and/or clinical data.

Patients’ data were subdivided in “responders (R)” (functional improvement of starting FEV$_1$, at least 12% and 200 ml, and clinical data improvement) and “no-responders (NR)” (stability or worsening of functional parameters) for mild, moderate, and severe stage.

Analysis of variance (ANOVA), mean, and standard deviation were performed to assess the best correlation between starting spirometric parameters (at the enrolment) and therapeutic response to inhaled salmeterol/fluticasone. Statistical analysis was performed for all measured functional parameters using GraphPad Prism version 4.00 for Windows, GraphPad software, San Diego California, USA.

**Results**

During the study 16 patients (5 moderate, and 11 severe) were withdrawn because of an acute exacerbation. At the end of treatment, 48 patients (18 mild, 21 moderate, and 9 severe) improved both functionally and clinically, 18 (3 mild, 7 moderate, and 8 severe) improved only functionally, 17 (8 mild, 7 moderate, and 2 severe) improved only clinically, and 71 (9 mild, 26 moderate, and 36 severe) didn’t improve (Table IV).

A FEV$_1$ improvement (+12% and 200 ml) was achieved in 21 mild, 28 moderate and 17 severe COPD patients, respectively 55.3%, 45.9%, and 30.9% of the population enrolled in this study (Figure 1).

![Figure 1](Therapeutic response for stage in 154 patients. During the study 16 out of 170 patients (5 moderate, and 11 severe) were withdrawn because of an acute exacerbation. A FEV$_1$ improvement was achieved after 12 weeks treatment in 55.3% of mild, 45.9% of moderate and 30.9% of severe COPD patients.)

Table IV. Therapeutic response

<table>
<thead>
<tr>
<th>Response and clinical</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
<th>Tot.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Functional</td>
<td>18</td>
<td>21</td>
<td>9</td>
<td>48</td>
</tr>
<tr>
<td>Functional</td>
<td>3</td>
<td>7</td>
<td>8</td>
<td>18</td>
</tr>
<tr>
<td>Clinical</td>
<td>8</td>
<td>7</td>
<td>2</td>
<td>17</td>
</tr>
<tr>
<td>No improvement</td>
<td>9</td>
<td>26</td>
<td>36</td>
<td>71</td>
</tr>
<tr>
<td>Withdrawal</td>
<td>5</td>
<td>11</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Tot.</td>
<td>38</td>
<td>66</td>
<td>66</td>
<td>170</td>
</tr>
</tbody>
</table>

Statistical analysis was performed to assess correlations between stage and therapeutic response.

A statistical difference in the percentage response between mild and moderate patients wasn’t significant ($p = 0.185$), whereas the difference between mild and severe patients appeared significant ($p = 0.010$) as well as between moderate and severe patients ($p = 0.049$) (Table V).

Moreover, the analysis of the starting functional parameters (before treatment) was carried out for the predictivity value in therapeutic response. As was to be expected, starting FEV$_1$% didn’t show a predictive value for therapeutic response of responders (R) and no-responders (NR) in the three stages (mild: 75.5% ± 3.4 in R, 76.1% ± 3.0 in NR, $p > 0.05$; moderate: 60.6% ± 5.6 in R, 57.8% ± 5.5 in NR, $p > 0.05$; severe: 43.5% ± 3.2 in R, 39.3% ± 7.0 in NR, $p > 0.05$) (Table VI).

A significant statistical difference was found for the following starting parameters: FEV$_1$/FVC, MEF50 and DLCO/VA% (diffusing capacity corrected for alveolar volume). Starting FEV$_1}$/FVC and MEF50 appeared to be significantly different with a bet-

<table>
<thead>
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<th>Table V. Responders for stage.</th>
</tr>
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<tbody>
<tr>
<td>Mild</td>
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<tr>
<td>Moderate</td>
</tr>
<tr>
<td>Severe</td>
</tr>
</tbody>
</table>

$p < 0.05$ (mild/moderate = 0.185, mild/severe = 0.01, moderate/severe = 0.049).
ter value for R in mild (FEV\textsubscript{1}/FVC: 65.8% ± 5 in R, 60.6% ± 6.5 in NR, \(p < 0.05\); MEF\textsubscript{50}: 39% ± 8.5 in R, 32.3% ± 4.9 in NR, \(p < 0.05\)) and moderate COPD patients (FEV\textsubscript{1}/FVC: 62.3% ± 5.1 in R, 55.1% ± 7 in NR, \(p < 0.05\); MEF\textsubscript{50}: 28.6% ± 5.6 in R, 23.9% ± 4.8 in NR, \(p < 0.05\)). In moderate (99.7% ± 14 in R, 84.9% ± 20.7 in NR, \(p < 0.05\)) and severe COPD patients (98.1% ± 23 in R, 81.5% ± 27 in NR, \(p < 0.05\)) a better starting value of DLCO/VA\% seems to be correlate with a probable therapeutic response to inhaled salmeterol/fluticasone (Table VI).

### Table VI. Predictive parameters value *\(p < 0.05\).

<table>
<thead>
<tr>
<th></th>
<th>Mild Responders</th>
<th>No-responders</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV\textsubscript{1}%</td>
<td>75.5% ± 3.4</td>
<td>76.1% ± 3.0</td>
</tr>
<tr>
<td>FEV\textsubscript{1}/FVC*</td>
<td>65.8% ± 5</td>
<td>60.6% ± 6.5</td>
</tr>
<tr>
<td>MEF\textsubscript{50}*</td>
<td>39% ± 8.5</td>
<td>32.3% ± 4.9</td>
</tr>
<tr>
<td><strong>Moderate</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEV\textsubscript{1}%</td>
<td>60.6% ± 5.6</td>
<td>57.8% ± 5.5</td>
</tr>
<tr>
<td>FEV\textsubscript{1}/FVC*</td>
<td>62.3% ± 5.1</td>
<td>55.1% ± 7</td>
</tr>
<tr>
<td>MEF\textsubscript{50}*</td>
<td>28.6% ± 5.6</td>
<td>23.9% ± 4.8</td>
</tr>
<tr>
<td>DLCO/VA%*</td>
<td>99.7% ± 14</td>
<td>84.9% ± 20.7</td>
</tr>
<tr>
<td><strong>Severe</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEV\textsubscript{1}%</td>
<td>43.5% ± 3.2</td>
<td>39.3% ± 7.0</td>
</tr>
<tr>
<td>DLCO/VA%*</td>
<td>98.1% ± 23</td>
<td>81.5% ± 27</td>
</tr>
</tbody>
</table>

*\(p < 0.05\)

Discussion

Pathophysiologic features of COPD airways include inflammation, airways obstruction, structural changes, and airways defence dysfunction. All these different features are relevant in determining the therapeutic response with the several COPD drugs.

The appropriate role of inhaled corticosteroids (ICS) in COPD is controversial. Inhaled steroid treatment in COPD may induce changes on some cellular and molecular parameters of airway inflammation. A number of short-term and long-term controlled trials, using ICS and evaluating clinical and functional parameters, have been published with conflicting results. The main long-term effect studies\textsuperscript{12,15} with ICS (EUROSCOP, Copenhagen City Lung Study, ISOLDE, Health Lung Study) reported no changes on the rate of FEV\textsubscript{1} decline\textsuperscript{12-15} and a decrease of exacerbations\textsuperscript{14,15}. The absence of physiological effects, as well as differences in inflammatory phenotype between COPD and asthma\textsuperscript{16}, has led many investigators to conclude that these drugs are ineffective in COPD.

A possible explanation for the effectiveness of ICS in COPD exacerbations is the finding that the pattern of bronchial inflammation changes during an exacerbation, showing an increase of airway eosinophils and mast cells, and airway eosinophilia is present in a subgroup of COPD patients who improve their pulmonary function in response to a short course of steroids\textsuperscript{17}.

Controversial data on the impact of ICS on airways inflammation in stable COPD were reported in many studies. Positive results reported a reduction in sputum of neutrophils\textsuperscript{16-20}, mucosal mast cells\textsuperscript{21,22}, IL-8\textsuperscript{23}, and an improvement in symptoms\textsuperscript{21,23}. Other studies didn't report clinical benefit in lung function, symptoms, or inflammatory parameters\textsuperscript{24,25}. For these reasons COPD guidelines recommend ICS only in exacerbations and severe stage\textsuperscript{14,26}.

However, in severe stage structural airways changes (loss of elastic recoil, alveolar destruction, fibrosis) are predominant, and the recoverable airways component could be less than early stage. Thus, the medical literature suggests that ICS provide clinical benefit to some patients with COPD and that this effect is independent of the patients' FEV\textsubscript{1} response, perhaps operating through an improvement in hyperinflation or a reduction in the frequency of exacerbations\textsuperscript{27}.

\(\beta_2\)-agonists and ICS have different effects in COPD response. \(\beta_2\)-agonists determine a functional response with bronchodilation. A major benefit of bronchodilator therapy is to improve lung emptying during expiration. This reduces dynamic hyperinflation at rest and during exercise and so improves exercise performance\textsuperscript{28}. A large body of scientific data confirms that long-acting \(\beta_2\)-agonists improve lung function and health status in stable COPD whilst also increasing the time between exacerbations\textsuperscript{28-31}.

Whereas ICS seem to determine a clinical response with decreased symptoms, exacerbation, and increased health status, all data quantifiable with difficulty. The variable effects of corticosteroids on airway inflamma-
tion may reflect the heterogeneity of the disease and also the reproducibility of markers of inflammation. Several long-term clinical trials supported the beneficial interactions between long-acting β₂-agonists and ICS in stable COPD patients. Improvement in symptoms, quality of life, and decrease in exacerbations were reported for long-term combination therapy in moderate-severe COPD. The combination therapies with salmeterol/fluticasone and formoterol/budesonide showed a significantly greater improvement than single drug alone. Unfortunately these trials were conducted only for moderate-severe stages, excluding mild stage.

This type of therapy not only improves airflow obstruction but also provides clinical benefits, influencing airway obstruction, mucociliary dysfunction, airways inflammation and in the least structural changes. The observed benefit from combining therapy seems to be due to a synergistic interaction. ICS may reverse the down-regulation of β₂-receptors by increasing the gene transcription of β₂-receptors and thus restoring the full responsiveness to β₂-agonists. The β₂-agonists induce CS-receptor (GR) translocation from the cytosol to the nucleus and enhance GR-CS response to a concomitant or subsequent challenge with ICS. Moreover, β₂-agonists can reduce bacterial adhesion to the epithelial cells lining the airways, reducing underlying inflammation and the frequency of infective exacerbations. The observation that the combination of inhaled corticosteroids and long-acting β₂-agonists is superior to placebo or either drug alone with regard to lung function, frequency of exacerbations, symptoms, and health status suggests that the use of inhaled corticosteroids should be restricted to patients in whom optimal bronchodilator therapy has failed to improve the symptoms, physiological findings, or frequency of exacerbations.

In our study we observed which COPD stage has the better response to the inhaled combination therapy with salmeterol/fluticasone and which starting functional parameters can show the best correlation with the response. Interestingly, the results showed a better response in mild and moderate stable COPD than in severe stage. The heterogeneous group of COPD patients in each stage contains several individual features about the type of airways inflammation, therapeutic sensitivity and airways remodelling. Presumably mild stage has a greater recovery capacity of progressive airway damage than severe stage, and combination therapy could promote this capacity.

The better response for mild and moderate stages, demonstrated as an improvement in the pulmonary function, is presumably observable when airways are not yet connected with fibrosis and emphysema. The autopsy data available seem to indicate that the predominant lesion in severe COPD is the parenchymal destruction, whereas in mild COPD the predominant lesion is the peripheral airways inflammation.

This study highlights the consideration of a careful pathophysiological assessment in COPD patient. For each patient not only FEV₁ value appears essential, but other functional parameters and clinical data too, as the new guidelines asserted. In the harder attempt to detect the predictivity of functional parameters to the response, our study confirmed the difference between the early and advanced stage of the disease. Starting (at the enrolment) FEV₁/FVC and MEF50 were significant predictors in mild and moderate stages, and starting DLCO/VA% resulted a significant predictor in moderate and severe stages.

Thus, in mild and moderate stages the predictive capacity appears tied to lung volume and flow. Whereas surprisingly, in severe stage, more characterised by emphysema and fibrosis, therapeutic response appears to be correlated with lung diffusion capacity. This is the first time that DLCO/VA% is correlate with therapeutic response in severe COPD. Diffusing capacity corrected for alveolar volume represents the situation of alveolar interstitium, a complex phenomenon involving the distributional relation of alveolar ventilation to alveolar capillary perfusion, and in these subjects it selects the responder subgroup more than other parameters.

These findings appear to divide COPD population in two large groups: subjects with FEV₁ > 50%, in whom responders subgroup shows a better FEV₁/FVC and MEF50 value, and subjects with FEV₁ < 50%, in whom the response is correlate with a better DLCO/VA% value.
Results from large studies on COPD provide evidence that regular treatment with these drugs is only appropriate for certain subgroups of patients with COPD\(^1\). In general, COPD patients with an acute response to ICS therapy have some features suggestive of asthma, but no study has identified reliable functional predictors of the lack of a response, and reversibility bronchodilator test results limited for identifying this subgroup. In fact all our patients had a negative reversibility test at the enrolment.

Our study is the first attempt to identify this functional correlation.

In conclusion, each COPD patient is different. The response to the inhaled combination therapy can depend on several factors (stage, concomitant diseases, method of inhalation, lifestyle). A need to identify the subgroup, within the large heterogeneous group of patients with COPD who benefit from treatment, is essential.

The results of this study and the discrepancy between mild and severe stage response would suggest the need for further, larger, and controlled studies to evaluate whether subgroups of patients can be identified in whom inhaled therapy may induce changes in clinical and functional parameters. In our study salmeterol/fluticasone improves FEV\(_1\)% in mild and moderate more than in severe COPD patients. A better management for early stage could really reduce the progression of the disease.

Potential predictive parameters, achieved in our study, may be considered in future long-term studies to validate these results in order to select patients for achieving the best therapeutic response. Significant functional parameters (static, dynamic, expiratory, inspiratory) should be considered in monitoring COPD patients, and not only FEV\(_1\).

A good proposal for a future study is a functional score of response, compound by significant predictive parameters, to evaluate before settling a COPD therapy. These findings may open new directions in the assessment, monitoring, staging, and treatment for mild, moderate and severe COPD patients.

We all agree that the aim of future research in pulmonology is to have the right means to individuate the features of each COPD patient to administer the best available therapeutic programme.

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