

# Significant gas-exchange improvements reported after roflumilast in two cases of severe COPD

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**ABSTRACT:** *Significant gas-exchange improvements reported after roflumilast in two cases of severe COPD. B. Sposato.*

Two cases of 63-year-old men with severe chronic obstructive pulmonary disease (COPD) associated with respiratory failure are presented. Both patients were treated with long acting bronchodilators, inhaled corticosteroids, theophylline, diuretics, long term oxygen therapy, and nocturnal non invasive mechanical ventila-

tion, without achieving any improvement or control of the disease course. We observed a clinical and functional improvement in both patients when we added roflumilast to the pharmacological treatment schedule. In this context, gas exchange parameters were greatly improved, leading us to speculate on the possible mechanisms causing such improvements in these COPD patients.

*Monaldi Arch Chest Dis 2013; 79: 3-4, Suppl., 45-48.*

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**Keywords:** *Roflumilast, COPD, Respiratory failure, Case report.*

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## Case Report 1

A 63-year-old man was suffering from severe chronic obstructive pulmonary disease (COPD) since 2003. In that year his forced expiratory volume in the first second (FEV<sub>1</sub>) was 40% of predicted and he was on

triple therapy, namely on high-dose inhaled corticosteroids (ICS, fluticasone 500 µg twice daily - bid), long-acting beta-agonist (LABA, salmeterol 50 µg bid), long-acting muscarinic antagonists (LAMA, tiotropium 18 µg once daily - od) and in addition short-acting beta agonist (SABA, salbutamol as re-

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*The work originated from the Unit of Pneumology, "Misericordia" Hospital, Via Senese 161, 58100 Grosseto, Italy, and has been supported by a grant from Takeda Italia SpA.*

*\* The author received a consultancy fee by Takeda Italia SpA for clinical data collection.*

*Editorial assistance was provided by Selene Mogavero, PhD and Colin G Egan, PhD (Primula Multimedia SrL) and was sponsored by Takeda Italia SpA.*

quired) oral theophylline and diuretics. The patient continued smoking until 2009, when he was hospitalized for severe respiratory failure due to a COPD exacerbation. Since then, the patient was put on long term oxygen therapy. In January 2009 arterial blood gas analysis (ABG), while the patient was breathing room air, showed a pulmonary arterial oxygen and carbon dioxide tension ( $\text{PaO}_2$  and  $\text{PaCO}_2$ ) of 60.3 mmHg and 49.4 mmHg, respectively. He also had a worsening of lung function ( $\text{FEV}_1 = 0.89$  L, 32% of predicted) and recurrent exacerbations (at least 2/year) of the disease that often led to hospitalizations. After a hospitalization in 2010 for hypercapnic respiratory failure, nocturnal non-invasive mechanical ventilation was also required. In 2010, ABG in room air showed further worsening of  $\text{PaO}_2$  and  $\text{PaCO}_2$  values (52.8 and 54.3 mmHg, respectively). The patient was compliant to pharmacological and non-pharmacological therapies. He also participated to pulmonary rehabilitation programmes in a specialized center during 2010 and 2012, with partial and temporary benefit. Despite  $\text{O}_2$  therapy, pharmacological therapy and nocturnal ventilation, the patient did not improve. In addition,

recurrent exacerbations causing two hospitalizations in 2010 and two in 2011, due to acute hypercapnic on chronic respiratory failure, were recorded.

In May 2012, the patient was prescribed roflumilast in addition to other pharmacological therapies, while theophylline was discontinued. Lung function tests, performed on the same day of treatment start, showed a  $\text{FEV}_1$  of 0.77 L (29% of predicted) and a  $\text{FEV}_1/\text{FVC}$  ratio of 46. ABG performed on oxygen therapy with a flow of 2L/min showed pH 7.37,  $\text{PaO}_2$  78.7 mmHg,  $\text{PaCO}_2$  53.6 mmHg. Treatment with roflumilast was followed by a rapid clinical and functional improvement: after 1-month, ABG on room air showed improvement of  $\text{PaO}_2$  (70.4 mmHg) and normalization of  $\text{PaCO}_2$  (43 mmHg).  $\text{O}_2$  therapy during the day was discontinued whereas it was maintained only during the night at a low flow (1,5 L/min) and associated to mechanical ventilation. After approximately 6 months from the beginning of treatment with roflumilast, ABG on room air showed  $\text{PaO}_2$  73.4 mmHg and  $\text{PaCO}_2$  49.4 mmHg,  $\text{FEV}_1$  0,85 L (33% of predicted) and  $\text{FEV}_1/\text{FVC}$  50. An overview of ABG values is presented in table 1.

Table 1. - Arterial blood gas analysis values recorded for the 2 presented cases

Date	Conditions	$\text{PaO}_2$ (mmHg)	$\text{PaCO}_2$ (mmHg)
<b>Case 1</b>			
January 2009	Room air	60.3	49.4
October 2010	Room air	52.8	54.3
May 2012 (roflumilast start)	Oxygen therapy with a 2L/min flow	78.7	53.6
June 2012	Room air	70.4	43
November 2012	Room air	73.4	49.4
<b>Case 2</b>			
May 2011	Oxygen therapy with a 2L/min flow	78.7	63.4
May 2012 (roflumilast start)	Oxygen therapy with a 2L/min flow	73.2	59.3
January 2013	Room air	71.9	43.6

## Case Report 2

A 63-year-old man, smoker until 2010, was diagnosed with severe COPD and hypercapnic respiratory failure. The patient was treated with high dose ICS/LABA combination therapy (budesonide 320 µg and formoterol 9 µg, bid), SABA (salbutamol as required), LAMA (tiotropium 18 µg od) and diuretics in addition to long term Oxygen therapy and nocturnal noninvasive mechanical ventilation. Since 2010 the patient reported numerous exacerbations (3-4/year) and was hospitalized at least twice each year in the intensive care unit, due to respiratory failure. Lung function tests in May 2011 showed: FEV<sub>1</sub> 0.74 L (24% of predicted); FEV<sub>1</sub>/FVC 26, PaO<sub>2</sub> 78.7 mmHg, PaCO<sub>2</sub> 63.4 mmHg while the patient was on O<sub>2</sub> therapy 2L/min.

In May 2012, after yet another hospitalization, roflumilast was prescribed. During the following 8 months there was a significant clinical improvement, mainly in dyspnea and exercise capacity. The patient did not experience any exacerbation and at the end of 8 months of treatment, ABG values on room air showed a PaO<sub>2</sub> of 71.9 mmHg and a normal PaCO<sub>2</sub> of 43.6 mmHg. An overview of ABG values is presented in table 1.

## Discussion

The above described cases are interesting examples of significant clinical and physiological improvements associated to the beginning and maintenance of pharmacological therapy with roflumilast in addition to conventional therapies in patients with severe COPD and respiratory failure.

MRC and NOTT studies demonstrated that long term oxygen therapy (>12-15 h/day) improved survival, quality of life (QoL) and pulmonary hypertension in patients with severe and irreversible airway obstruction (FEV<sub>1</sub> less than 1.5 L) and hypoxemia (PaO<sub>2</sub> <55 mmHg) [1, 2].

In both reported cases, oxygen therapy was only able to partially normalize PaO<sub>2</sub> values. During the two years of long term oxygen therapy, the patients continued to have frequent exacerbations and hospitalizations. Also other combination treatments with bronchodilators, ICS and theophylline, as recommended by guidelines [3], did not seem to provide further beneficial effects. When Roflumilast was added to other treatments the patient clinically improved. In this context, both patients showed important changes in gas exchange parameters associated with roflumilast therapy.

Among the drugs used for COPD therapy, LABA may lead to a temporary reduction of PaO<sub>2</sub> in COPD patients, probably due to the decreased ventilation/perfusion ratio subsequent to the increased bronchodilation (and blood flow) in poorly ventilated areas [4]. Tiotropium seems to have a better safety profile, causing minor changes in blood-gas pressure and therefore has a potentially lower risk of worsening hypoxia [5].

On the contrary, the use of corticosteroids (both inhaled and systemic) seems to increase, or at least inhibit, the transient fall in PaO<sub>2</sub> induced by LABA and reduce the PaCO<sub>2</sub>, resulting in improved levels of hemoglobin saturation [4].

No real clinical experience nor clinical studies conducted so far have shown such an evident effect of roflumilast treatment on gas exchange parameters.

The two described cases are of great interest due to the obvious effect of treatment with roflumilast in patients characterized by hypoxemic-hypercapnic respiratory failure caused by severe COPD. These patients have a reduced survival, severe respiratory disability and poor QoL [3]. Any intervention able to change this devastating condition has to be taken into account.

The improvements in gas exchange parameters after roflumilast therapy could be related to a better ventilation/perfusion ratio. It seems reasonable to link this effect to the

known anti-inflammatory effects of roflumilast into the airways. In this regard, it should be noted that this phenomenon could also be related to the activities of corticosteroids on the PaO<sub>2</sub> values in patients with COPD. Corticosteroids act through a number of molecular mechanisms different to roflumilast and could induce a preferential circulation in the most ventilated areas and optimize the ventilation/perfusion ratio [4].

It is possible to speculate the presence of an additional synergistic effect of ICS combined to roflumilast on ventilation/perfusion ratio through an airway anti-inflammatory effect expressed at different levels of the inflammatory process from two medications taken in combination, as it was the case of our patients. Further studies are needed to understand the relationship between the inhibition of the roflumilast target PDE4 and the potential effect on the ventilation/perfusion ratio.

### **Riassunto**

*Sono di seguito presentati due casi clinici di pazienti con broncopneumopatia cronica ostruttiva (BPCO) associata a insufficienza respiratoria. Entrambi i pazienti avevano 63 anni e venivano trattati con broncodilatatori a lunga durata, corticosteroidi per via inalatoria, teofillina, diuretici, ossigeno terapia a lungo termine e ventilazione meccanica notturna non invasiva senza raggiungere alcun miglioramento o controllo soddisfacente della malattia. Quando si aggiungeva*

*roflumilast alla terapia, si osservava un miglioramento delle condizioni cliniche e delle funzionalità polmonari in entrambi i pazienti. In questo contesto, i parametri di scambi gassosi miglioravano notevolmente, portando a speculare sui possibili meccanismi alla base di tali miglioramenti in questi pazienti affetti da BPCO.*

*Parole chiave: Roflumilast, BPCO, Insufficienza respiratoria, Caso clinico.*

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