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The effect of Roflumilast in addition to LABA/LAMA/ICS treatment in COPD patients.

Novel insight using functional respiratory imaging

Wilfried De Backer, MD[1]; Wim Vos[2], PhD; Cedric Van Holsbeke[2], Msc; Samir Vinchurkar, PhD[2]; Rita Claes[1], Annemie Hufkens[1], Paul M. Parizel, MD[3]; Lieven Bedert[4], MD; Jan De Backer, PhD[2]

[1] University Hospital Antwerp, Department of Respiratory Medicine, Belgium

[2] Fluidda nv, Belgium

[3] University Hospital Antwerp, Department of Radiology, Belgium

[4] ZNA, Department of Respiratory Medicine, Belgium

Corresponding author

Jan De Backer

Groeningenlei 132

2550 Kontich

Belgium

Tel +32 3 450 87 20

Fax +32 3 450 87 29

Jan.DeBacker@Fluidda.com

Disclosure

This study was funded by Takeda. Given the opportunity to review draft and final versions of the manuscript, Takeda provided comments. However, consideration of these comments remained at the full discretion of the authors.

WDB is director and JDB is shareholder/CEO of Fluidda nv, a company that develops and markets part of the technology described in this paper. WV, CVH and SV are employees of Fluidda nv.

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Conception or design of the work: WDB, WV, LB, JDB

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Drafting or revising: WDB WV CVH SV RC AH PP LB JDB

Final approval: WDB WV CVH SV RC AH PP LB JDB

Accountable for content: WDB WV CVH SV RC AH PP LB JDB

Abstract

Rationale

The current study aims to assess the mode of action of Roflumilast as an add-on to LABA/LAMA/ICS therapy in severe COPD patients and to identify responder characteristics.

Methods

Forty-one patients were randomized to receive roflumilast or a placebo. At baseline and after 6 months of treatment, pulmonary function tests, exercise tolerance tests and functional respiratory imaging (FRI) were performed and patient reported outcomes (PRO) were measured.

Results

A significant improvement in FEV1 of 66±120 ml was observed in the roflumilast group compared to baseline. In the placebo group the FEV1 declined by -59±71 ml. The response was driven by a 8 responders with a change in FEV1 larger than 120ml. The responders experienced worse dynamic hyperinflation during exercise at baseline compared to non-responders. FRI parameters indicated regional changes in hyperinflation after treatment with roflumilast leading to an improvement in PFT, PRO and exercise tolerance.

Conclusions

The anti-inflammatory characteristics of Roflumilast reduce inflammation in the smaller airways, leading to a reduction in hyperinflation, a change in internal airflow distribution and alteration of the deposition of the LABA/LAMA/ICS therapy leading to clinical improvements. Patients who suffer from dynamic hyperinflation tend to benefit from Roflumilast.

Funding

This study was funded by Takeda.

Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by a combination of chronic inflammation of the smaller airways and destruction of lung tissue leading to the formation of emphysematous regions. The disease is most often classified according to The Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines (1). The baseline therapies for COPD are bronchodilators (Beta2 agonists, anticholinergics, theophylline or a combination of these). For the more severe COPD patients with a forced expiratory volume in one second (FEV1) below 60% predicted, inhaled corticosteroids are added to the treatment plan. Recently Roflumilast has been added as a therapeutic option. Roflumilast is a selective phosphodiesterase type 4 (PDE4) inhibitor (2). PDE4 regulates cyclic adenosine monophosphate (cAMP) in most of the cell types that are involved in inflammatory processes. Inhibition of PDE4 reduces the breakdown of cAMP, which in turn down-regulates the inflammatory process. In vitro and in vivo studies have confirmed the anti-inflammatory capabilities of the compound in terms of reducing the circulating TNF-α; the TNF-α in bronchoalveolar lavage (BAL), which acts as a pro-inflammatory mediator; and increased interleukin 10 (IL-10), an anti-inflammatory mediator. Two large-scale clinical trials (3, 4) have assessed the clinical efficacy of Roflumilast in terms of improving or stabilizing FEV1 and reducing exacerbations. Although in general the results were positive (i.e. 48 ml FEV1 improvement compared to a placebo and 0·83 rate ratio for exacerbations in favor of roflumilast compared to the placebo), a number of concerns were formulated by the regulatory and scientific bodies. The main concern was that the current studies did not assess the effect of Roflumilast in addition to a combination product such as long acting beta2 agonists (LABA) or long acting muscarinic agents (LAMA) combined with inhaled corticosteroids (ICS) (5). This remark formed the basis of the REACT study, which is aimed at examining the effect of Roflumilast as an add-on to LABA/ICS combination therapy (6). Experts also recognized the shortcomings of FEV1 as primary endpoint, specifically to assess anti-inflammatory compounds (5). While exacerbations are highly clinically relevant, the use of exacerbations as endpoint in clinical in itself poses a number of challenges. Firstly, the COPD guidelines define an exacerbation as “an acute event characterized by a worsening of the patient’s respiratory symptoms that is beyond normal day-to-day variations and leads to a change in medication”. This definition, however, is very broad and relies on the subjective interpretation of

the treating physician. Secondly, to assess changes in this endpoint during a clinical trial, one needs to have a sufficiently large base of exacerbations to start from in order to see any improvement. This means that either investigators have to rely on historic data to know the patient's exacerbation rate or the clinical trial duration must be sufficiently long to establish a baseline exacerbation rate. The latter seems unrealistic. Comparing the exacerbations rates between the treated and the placebo group, as was done in the two large-scale trials using Roflumilast (3, 4), is an option. But as could be seen from the data, the difference in absolute terms is often small (i.e. from 1·37 exacerbations per patient to 1·14 exacerbations per patient), making it hard to extrapolate the clinical relevance.

Recently, a high-resolution CT-based imaging method called functional respiratory imaging (FRI) has been developed. The technology defines in greater detail lung geometry and regional changes in airway volume and resistance. By assessing changes close to the site of action of the intervention (e.g. bronchodilation or reduction in inflammation), the method is more sensitive compared with the standard pulmonary function tests (7). This implies that the mode of action of an intervention can be assessed in a small number of patients while maintaining sufficient power to have statistically significant results. More subtle changes in airways, for instance due to reduction in inflammation after a long term treatment, could be detected using FRI. The method has been validated using gamma scintigraphy (8) and single photon emission computed tomography (SPECT) CT (9). The clinical relevance has been demonstrated by correlating image-based outcome parameters such as the change in FRI-based airway volume (iVaw) and FRI-based airway resistance (iRaw) with conventional pulmonary function tests (PFT) such as a FEV1 (7) and FEV1/FVC (10). Significant correlations have been found between FRI-based parameters and patient reported outcome parameters (PRO) (11).

The aim of the current study was to investigate the mode of action of Roflumilast in COPD patients on top of triple therapy (LABA/LAMA/ICS) using PFT, exercise tolerance tests, PRO and FRI. The hypothesis was that Roflumilast provides a large benefit to a subset of COPD patients and that FRI can assist in phenotyping these (strong) responders. Ideally a PFT parameter could be defined that could identify the responding phenotype.

Methods and Materials

A total of 41 COPD patients has been included from January 2012 until October 2012 in two clinical centers. To be considered for the study, the patients had to meet the criteria described in Table 1. Patients were block randomized with a ratio of 3 treated to 1 placebo control subject to eliminate any seasonal influences. The study consisted of two visits, one at baseline and one after 6 months of treatment with either Roflumilast (500mcg tablet, once daily) or a placebo.

During these two visits, the following tests were performed post bronchodilation:

- Spirometry
- Body plethysmography
- 6 minute walk test
- Patient reported outcomes
- Forced Oscillation Technique (FOT)
- Functional Respiratory Imaging (FRI)

The FRI parameters were derived from low-dose CT scans at total lung capacity (TLC) and functional residual capacity (FRC). Segmentation principles allowed quantification and visualization of the lung, lobar and airway volumes. Computational Fluid Dynamics (CFD) was used to determine the airway resistance. FRI outcome parameters included:

- Lobar volume at TLC (iLobes_TLC)
- Lobar volume at FRC (iLobes_FRC)
- Image based airway volume at TLC (iVaw)
- Image based airway resistance at TLC (iRaw)

More details and validation of FRI can be found in De Backer et al (9).

Statistical analysis

Statistical analysis was performed using R 2·15·3. Changes in individual parameters after 6 months of treatment with the study medication or placebo were evaluated using Wilcoxon matched pairs analysis.

Correlations between the changes in different parameters were evaluated using Spearman correlations. All statistical tests were considered significant when $p < 0{\cdot}05$. The sample size of this exploratory study was determined based on previous studies using similar FRI endpoints(7, 11). All statistical analyses were performed on the 32 evaluated patients.

Ethics

The study was approved by the ethical commissions of all participating centers. All patients signed an informed consent (NCT01480661).

Results

A CONSORT diagram (Figure 1) outlines the workflow for the study. Out of 41 patients, 32 patients completed all visits, 9 patients dropped out of the study. The baseline characteristics of both groups can be found in

Table 2.

A significant improvement in FEV1 was observed compared to baseline (p = 0·01) with an increase of 66 ± 120 ml and compared to a placebo (p = 0·006). In the placebo group, the FEV1 declined by -59 ± 71 ml, which was borderline significant compared to baseline (p=0·052) (Figure 2).

In the Roflumilast treatment arm, 8 patients (35%) exhibited an FEV1 improvement by more than the measurement accuracy of FEV1, which was recently determined to be 120ml (12). In this group of responders, the average increase in FEV1 was 186·25 ± 6·76 ml. In order to gain insight into the phenotype of the responder other parameters were assessed where the responders differed from the other patients. When assessing the results of the exercise tolerance test, responders were considered to be patients who felt significantly (p = 0·013, Borg Fatigue score) worse after the 6-minute walk test (6MWT) performed at baseline compared to the non-responders. The Borg fatigue score after the 6MWT at baseline was 5·60 ± 1·52 for patients with an improvement in FEV1 > 120ml. The Borg fatigue score for the other patients after 6MWT at baseline was 2·41 ± 2·29 (Figure 3). When assessing the hyperinflation in terms of lobar volumes, it could be observed that the image based lobar volumes at FRC (iLobes_FRC) in the responders were reduced significantly (-1·98 ± 9·88 %, p=0·023) after 6 months of treatment with Roflumilast compared to the other patients in the group whose iLobes_FRC increased by 3·09 ± 10·12%. The iLobes_FRC in the placebo group increased by 7·11± 13·80%, which was significantly different from the responders (p=0·003) but not significantly different from the other treated patients (p=0·16) (Figure 4). The responders improved in terms of the 6MWT by 48·5 ± 38·0 m, which was significantly different from the other treated patients (p=0·039), who only improved 6·54 ± 46·54m, and with the placebo group (p=0·012) who did, on average, worse on the 6MWT -27·63 ± 41·76 (Figure 5). There was significantly (p < 0·0001) more bronchodilation in terms of image-based airway volume (iVaw) in the responders compared to the other patients (Figure 6). The iVaw in the responders increased on average 19·50 ± 38·58 % while the in the other patients, the iVaw was reduced by 11·53 ± 8·46%. The fact that the groups were significantly different (p < 0·0001) (Figure 7 and Figure 8) graphically illustrates the changes in iVaw for a patient responding to the Roflumilast treatment versus one

patient who does not respond to the therapy. At the same time, the image based resistance (iRaw) improved in the responder group (-24·31± 28·52%), which was significantly different ($p < 0·0001$) from the other patients whose iRaw increased by 66·18 ± 73·52% (Figure 9).

A significant weight loss of 4·70 ± 3·11 kg was observed in the group treated with Roflumilast compared to baseline ($p < 0·0001$) and compared with the placebo group ($p = 0·0003$). The placebo group did not significantly lose weight during the 6 month treatment period ($p = 0·73$). A significant correlation ($R=0·46$, $p=0·025$) was found between the baseline BMI and the weight loss after treatment, as patients with a larger BMI at the beginning of the study tended to lose the most weight (Figure 11**Fout! Verwijzingsbron niet gevonden.**).

Discussion

It is clear that the next generation of novel drugs for respiratory diseases, both asthma and COPD, is targeted at reducing inflammation in the airways. While proof of concept studies have demonstrated the potential benefit of these compounds, it remains challenging to identify the mode of action, the time to onset and the responder phenotype. Conventional PFT lacks the sensitivity to detect these subtle changes while monitoring exacerbation rates is time consuming and subject to interpretation. The current study confirmed the potential of PDE4 inhibitors to improve lung function in COPD patients even when administered in addition to triple (LABA/LAMA/ICS) therapy, which has never been previously studied. At the same time, the FRI outcome parameters were able to provide a hypothesis for the mode of action of Roflumilast leading to the improvements observed in the lung function. It appears that the patients who are doing well when using this PDE4 inhibitor are the patients who are prone to dynamic hyperinflation as indicated by the PRO after the 6MWT. Apparently, treating these patients with Roflumilast reduced inflammation in the smaller airways, resulting in an improvement in the regional (lobar) hyperinflation as measured by FRI. Given that the product was administered orally, we could speculate that the effective site of action was different compared to the site of action of the standard of care inhalation therapy. Local changes in inspiratory capacity resulted in an improvement in exercise tolerance. Small improvements in air trapping and pulse oximetry were previously described by O'Donnell et al (13). The authors, in contrast to the current study, did not report an improvement in hyperinflation. It must be noted that the improvement in regional hyperinflation that we observed was measured on a lobar level using the CT data. Also, when we assessed the change in global lung level, we did not observe a change in hyperinflation. This can be explained by the fact that the lung lobes are interdependent, so if one lobe is reduced in hyperinflation, the neighboring lobe potentially re-inflates, thereby reducing the overall signal. However, when looking at the individual lobes, these signals could be detected and their clinical relevance could be assessed. While Roflumilast's anti-inflammatory effect might cause a reduction in hyperinflation and consequently an improvement in the patient's clinical condition, it is unlikely that this effect alone causes the large improvements in FEV1 seen in the responder subgroup. A more likely explanation can be found when assessing the change in internal airflow distribution. FRI parameters allow assessment of the lobe

expansion from expiration to inspiration and hence can indicate the ventilation rate on a lobar level. Changes in lobar characteristics such as hyperinflation will cause a shift in the internal airflow distribution. This also implies that the deposition of the triple therapy changes. Therefore, the significant improvement in FEV1 is more likely to be an effect of enhanced efficacy of the inhalation therapy rather than an effect of the PDE4 inhibitor by itself. Assessing the changes in iVaw and iRaw for the responding subgroup further supports this statement. A previous imaging study by De Backer et al. using FRI assessed the effect of a LABA/ICS combination in COPD patients (7). The changes in iVaw and iRaw, hence the bronchodilation, observed in the current study are in the same order of magnitude as the effect of the LABA/ICS combination observed by De Backer et al. Potentially the exercise tolerance tests in combination with patient reported outcome parameters could be used at baseline to screen for responders. The relative ease and low cost of these tests facilitates the practical implementation.

Even though the mode of action of the product appears to be clear when assessing the different parameters, this study still has some limitations. The sample size is relatively small and the placebo group was smaller than the actively treated group. The latter was the result of ethical considerations since Roflumilast is part of the current treatment options and we decided not to prevent a large group of patients from receiving the drug. Despite the small sample size, it appeared that the study was not underpowered. Previous studies using sensitive FRI endpoints were also performed in small sample sizes while maintaining statistical significance (7, 11, 14). CT-based FRI parameters involve the use of ionizing radiation with potential adverse effects. However, in this study the radiation dose was reduced by applying dose reduction protocols well described in the literature (15). This ensures that the total dose to the patient is limited to the equivalent of a maximum of one and a half standard CT thorax scans. Considering the vast amount of quantifiable information that can be obtained from FRI, the use of the method in early clinical trials is very defensible, especially when it can complement and enhance the interpretation of the classical PFT parameters. In conclusion, we can state that the current study, for the first time, allowed the assessment of the mode of action of the only PDE4 inhibitor currently used in clinical practice. By using novel endpoints in combination with classical pulmonary function tests, hypotheses could be generated and tested to understand the interaction of the systemic and oral medication and to start responder phenotyping. These possibilities create significant future opportunities to gain better insight into the mechanism of novel drugs

and to select the appropriate patient population.

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Tables

Table 1: In- and exclusion criteria

INCLUSION CRITERIA
• Male or female patient ≥ 30 years old • Patient with BMI ≥ 20 • Female patient of childbearing potential who confirms that a contraception method was used at least 14 days before visit 1 and will continue to use a contraception method during the study. • Patient should be treated according to GOLD guidelines • COPD patient with GOLD stages III until IV • Patient with smoking history of at least 10 pack-years • Patient takes Spiriva® and a fixed combination of inhaled steroids and LABA at least 6 weeks before visit 1 • Patient must be able to understand and complete the protocol requirements, instructions, questionnaires and protocol-stated restrictions. Patient should give informed consent.
EXCLUSION CRITERIA
• Pregnant or lactating females • Patient with severe immunological diseases and/ or severe acute infectious diseases. • Patient with heart failure • Patient with diagnosis of cancer (except basal cell carcinoma) • Patient with a history of depression associated with suicidal ideation or behavior • Patient with moderate or severe hepatic impairment. • Patient with lactose intolerance • Patient who is unlikely to comply with the protocol or unable to understand the nature, scope and possible consequences of the study. • Patient who received any investigational new drug within the last 4 weeks prior to the baseline visit or twice the duration of the biological effect of any drug (whichever is longer).

Table 2: Baseline characteristics for the treated (n=23) and placebo (n=9) group

	Roflumilast	placebo
Length (cm)	166.2±6.44	170.06±10.56
Packyears (years)	53.13±35.57	54.83±30.24
Age (years)	63.61±7.38	70±6.76
Weight (kg)	84.08±28.58	92.81±26.18
FVC (%pred)	79.76±21.08	79.97±13.43
FEV1 (%pred)	41.3±12.17	47.28±11.19
FEV1/FVC (%)	42.5±12.62	46.61±10.41
RV (%pred)	171.32±35.31	146.36±28.26
TLC (%pred)	114.44±21.39	106.22±11.02
FRC (%pred)	147.22±33.72	130.94±25.07
Raw (kPas/L)	0.77±0.3	0.67±0.35
sRaw (kPas)	3.97±1.96	3±1.26
LCI (-)	8.87±1.33	9.16±1.94
N2 washout time (min)	5.48±2.51	3.46±1.16
6MWT (m)	357.53±90.02	403.88±148.84

Figures

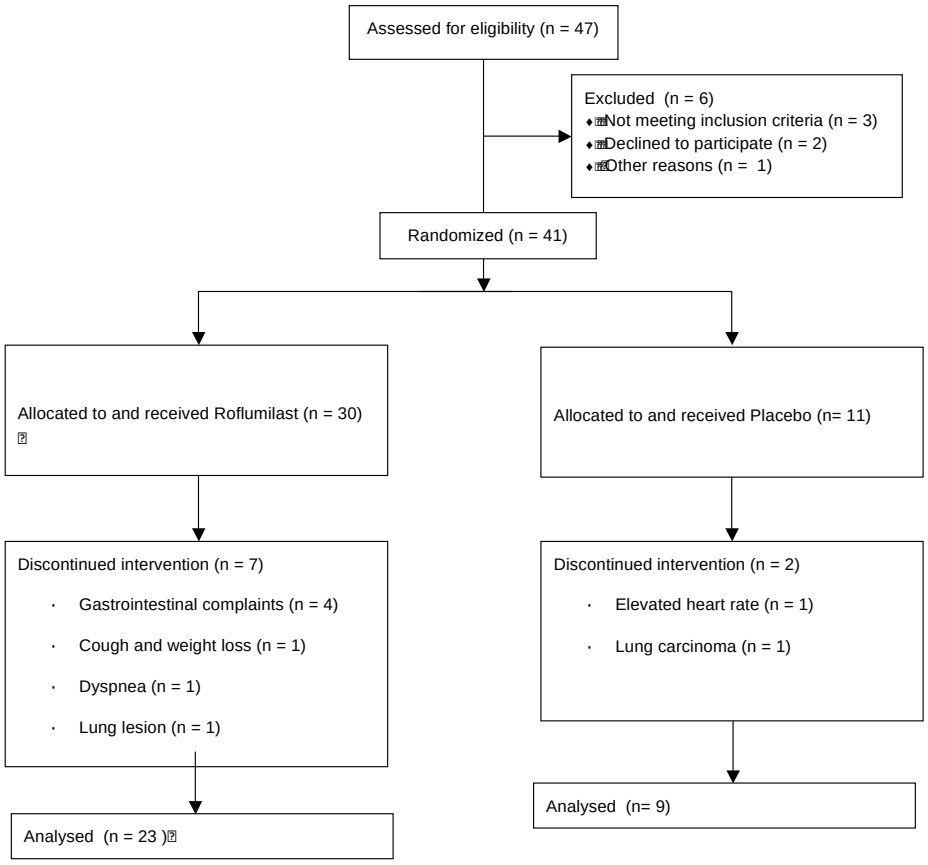

Figure 1: CONSORT flow diagram of the study.

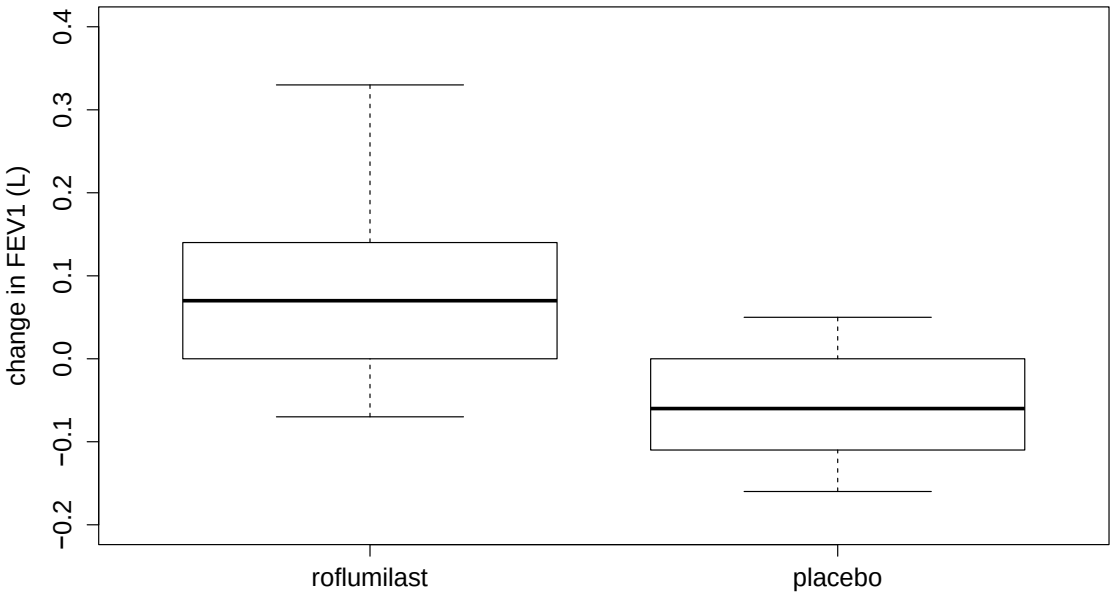

Figure 2: significant improvement with Roflumilast in FEV1 compared to baseline (p = 0.01) and compared to placebo (p = 0.006); borderline significant drop in FEV1 in the placebo group compared to baseline (p=0.052).

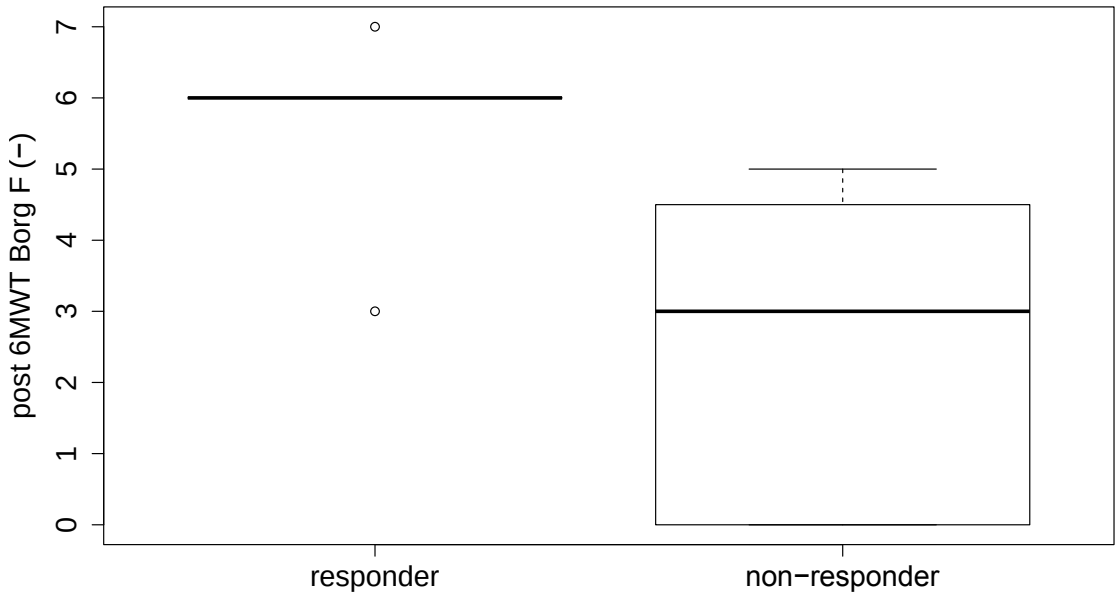

Figure 3: Borg fatigue score after 6MWT at baseline; significant difference between the responders (FEV1>5%) and the other patients (p = 0.013)

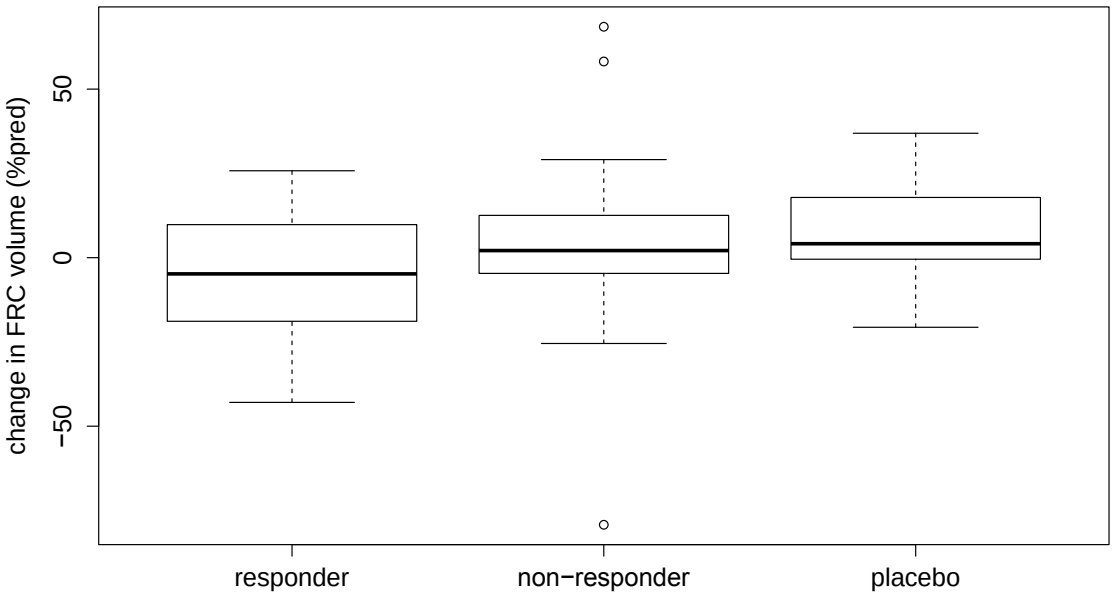

Figure 4: significant reduction in iLobes_FRC (p=0.023) after 6 months of treatment with Roflumilast in the responder group (FEV1>5%) compared to the other patients in the group;, iLobes_FRC in the placebo group increased significantly compared to the responders (p=0.003) but not compared to the other treated patients (p=0.16).

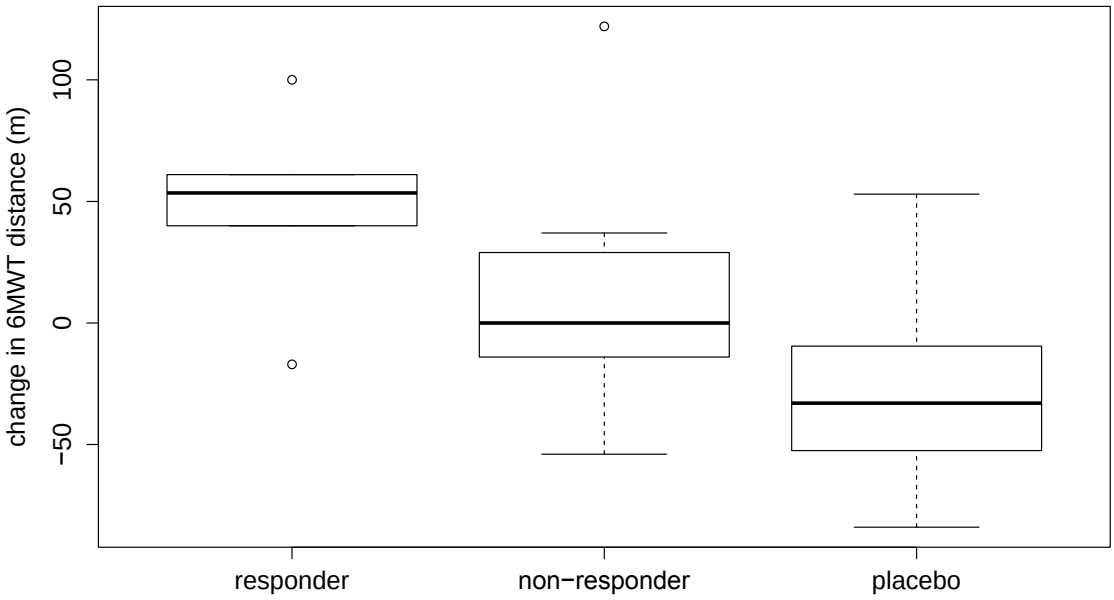

Figure 5: Significant improvement in 6MWT in the responder group (FEV1>5%) compared to the other treated patients (p=0.039) and compared with the placebo group (p=0.012).

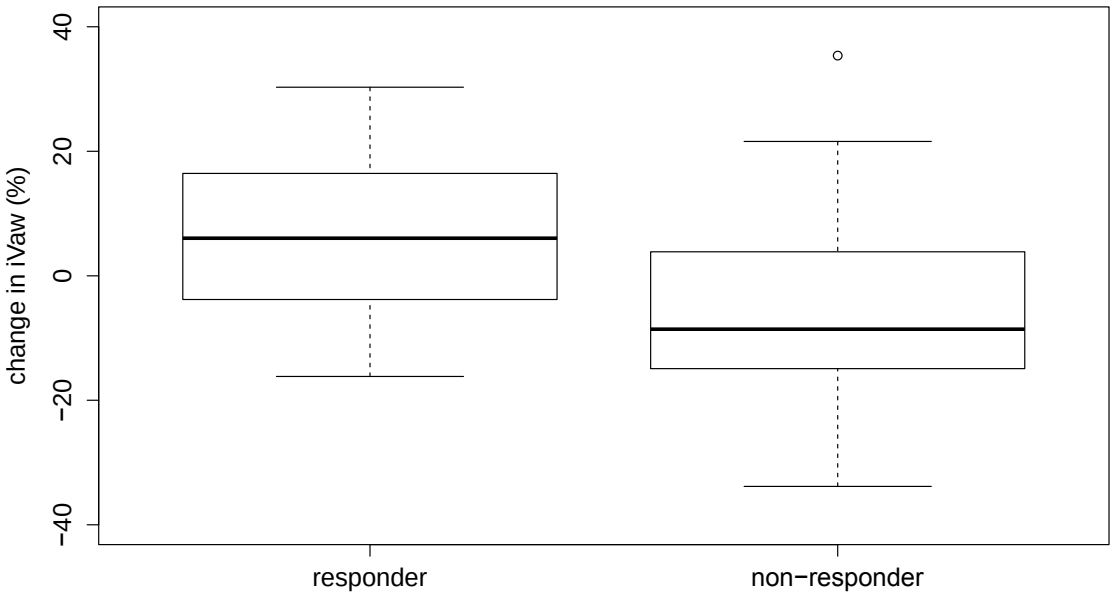

Figure 6: Significant ($p < 0.0001$) increase in bronchodilation in terms of image-based airway volume (iVaw) in the responders (FEV1>5%) compared to the other patients.

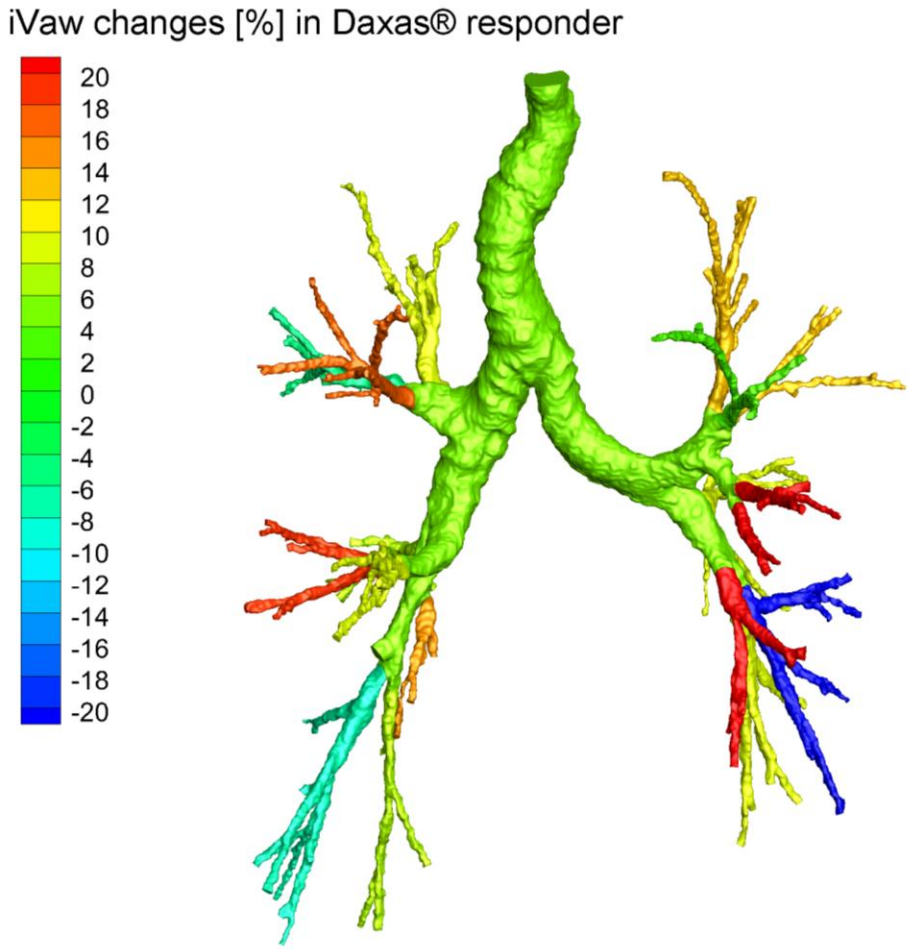

Figure 7: Changes in iVaw in a patient with a large response (FEV1 > 5%) to the Roflumilast treatment

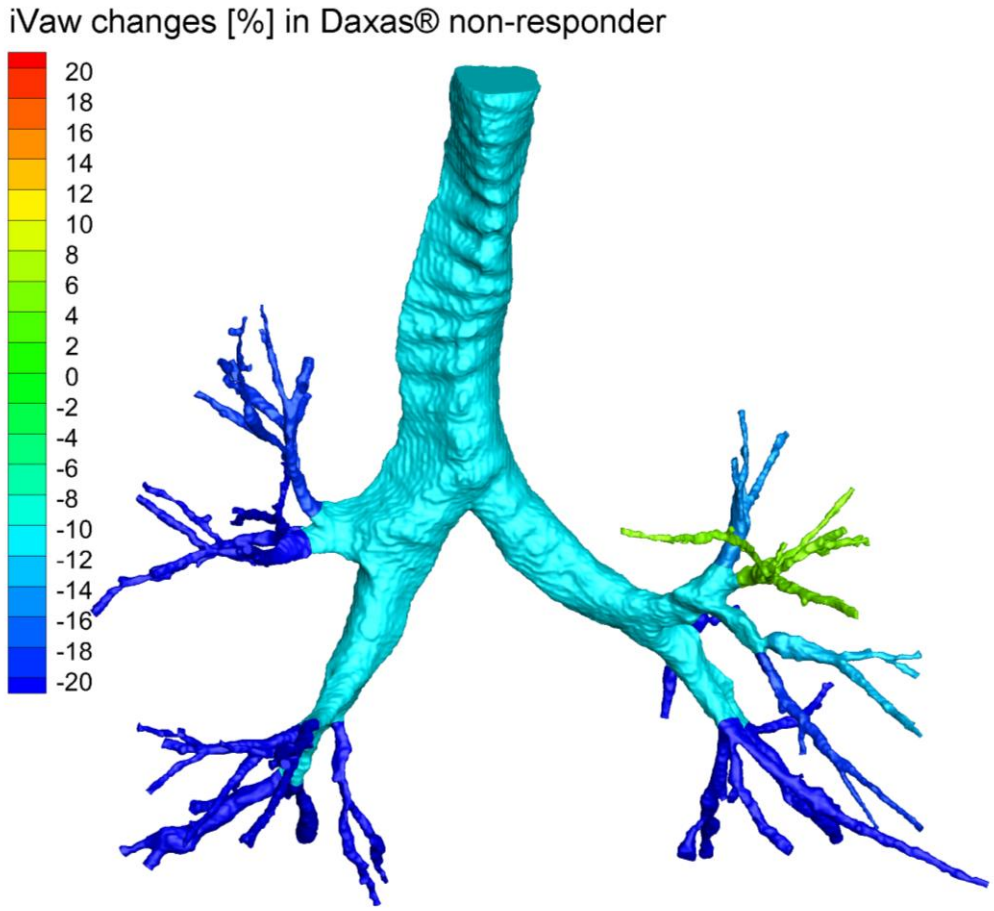

Figure 8: Changes in iVaw in a patient with no response (FEV1 > 5%) to the Roflumilast treatment

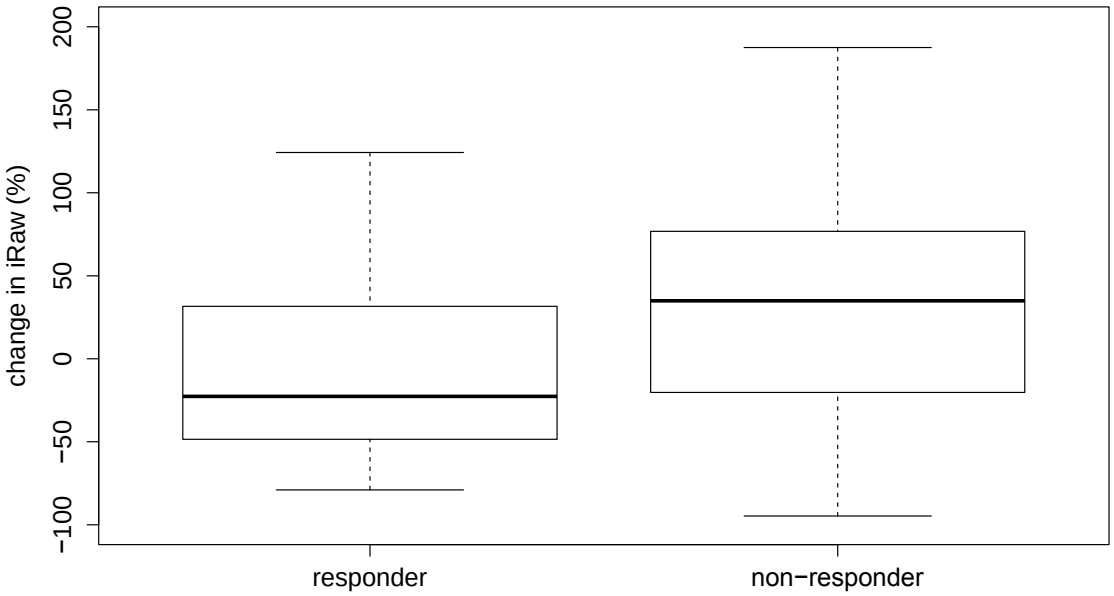

Figure 9: Significant difference between the change in iRaw in the responder (FEV1>5%) group compared to the other patients.

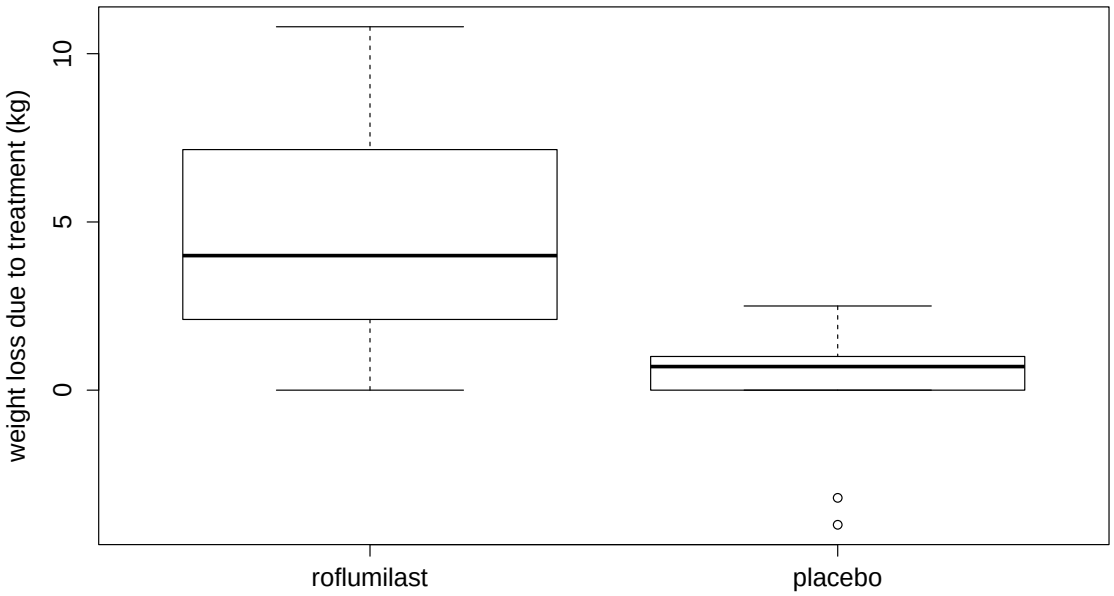

Figure 10: significant weight loss in the group treated with Roflumilast compared to baseline ($p < 0.0001$) and compared to the placebo group ($p = 0.0003$); no significant weight loss during the 6 month treatment period with placebo ($p = 0.73$).

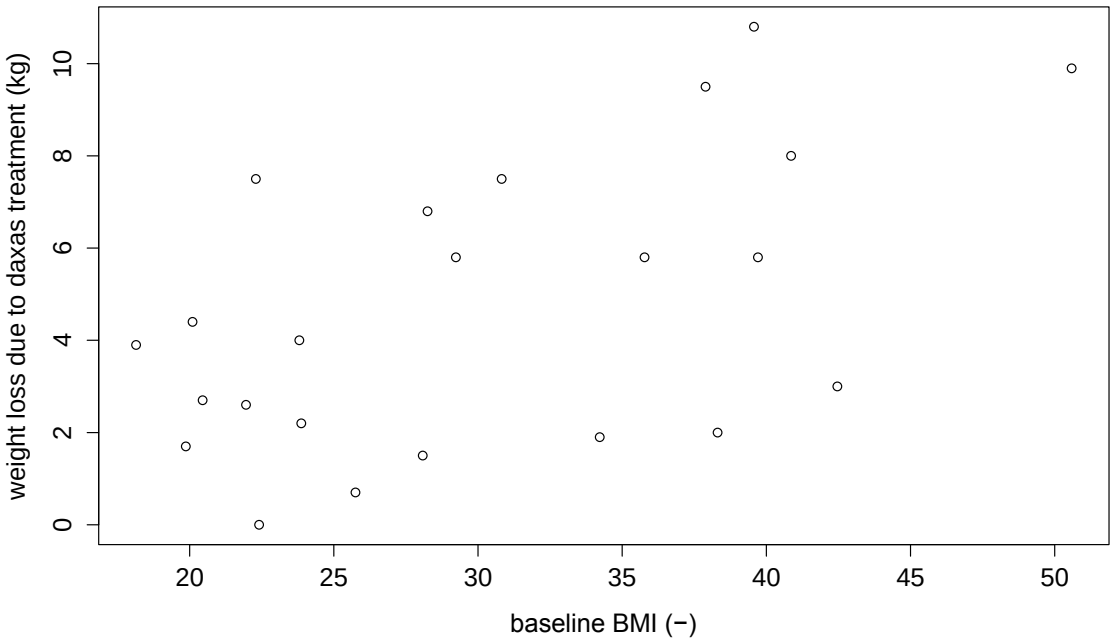

Figure 11: significant correlation (R=0.46, p=0.025) between baseline BMI and the weight loss after treatment with Roflumilast