

Functional Respiratory Imaging (FRI) to assess the mode of action and responder phenotype of Roflumilast

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Background

Roflumilast (Daxas®, Takeda) is a selective phosphodiesterase type 4 (PDE4). Recently Roflumilast has been added as a therapeutic option for severe COPD patients. While the product seems to reduce the number of exacerbations in COPD patients, a number of questions remain the topic of ongoing research. In particular the interaction between the orally administered Roflumilast and concomitant medication such as the standard of care inhalation therapy needs further research. The inhalation therapy in COPD patients is often a combination of long acting beta 2 agonist (LABA), long acting anti-muscarinic agents (LAMA) and inhaled corticosteroids (ICS). One of the main challenges in developing novel anti-inflammatory compounds such as Roflumilast is that the current gold standard endpoints such as the forced expiratory volume in one second (FEV1) lack the sensitivity to detect subtle differences in the respiratory system. A novel image method called Functional Respiratory Imaging or FRI allows detecting changes in the lungs and airways with higher accuracy and hence could be used to describe the effect of anti-inflammatory interventions. The current study therefore aims to assess the mode of action of Roflumilast as ad-on to LABA/LAMA/ICS therapy in severe COPD patients. In addition the study aims to identify the characteristics of the responders.

Methods

Forty-one patients were randomized to receive roflumilast or 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.

Findings

A significant improvement in FEV1 of 66 ± 120 ml ($p = 0.01$) was observed in the roflumilast group compared to baseline. The response was driven by a subset ($n=8$) of responders with a change in FEV1 exceeding the measurement error of FEV1 recently determined to be 120ml. The responders experienced worse dynamic hyperinflation during exercise at baseline compared to the non-responders. FRI parameters indicated regional changes in hyperinflation after treatment

with roflumilast leading to an improvement in PFT, PRO and exercise tolerance (Figure 1 & Figure 2).

Interpretation

The anti-inflammatory characteristics of Roflumilast seem to reduce inflammation in the smaller airways leading to a reduction in hyperinflation. The reduction in hyperinflation appears to be associated with an improved ventilation of these areas, hence more air is going to lobes that experience a reduction in air trapping. Consequently the internal airflow distribution (IAD) changes in the responding patients. The change in IAD enhances the deposition of the LABA/LAMA/ICS therapy. Areas that are better ventilated also receive more inhaled particles, since inhaled particles tend to follow the internal airflow. Since particles are now reaching other, previously undertreated areas, clinical improvements can be observed in terms of improved FEV1, improved 6 minute walking distance and significantly more FRI based bronchodilation. Patients, who suffer from dynamic hyperinflation at baseline, tend to benefit most from Roflumilast. Most likely these patients have the largest amount of sub-optimally treated regions in the lungs. The findings of the current study are relevant for two main reasons. Firstly the current study is the first study to report the effect of a PDE4 inhibitor in addition to ICS/LABA/LAMA therapy. Secondly more sensitive, image-based endpoints provide additional insights into the mode of action of anti-inflammatory compounds and provide a basis for responder phenotyping. The latter will be important when considering the development of novel, often expensive anti-inflammatory compounds for respiratory diseases. The current study provides hypotheses that need to be confirmed in larger clinical trials.

Funding

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Reference

The effect of roflumilast in addition to LABA/LAMA/ICS treatment in COPD patients.
De Backer W, Vos W, Van Holsbeke C, Vinchurkar S, Claes R, Hufkens A, Parizel PM, Bedert L, De Backer J.
Eur Respir J. 2014 May 2.

Figures

iVaw changes [%] in Daxas® responder

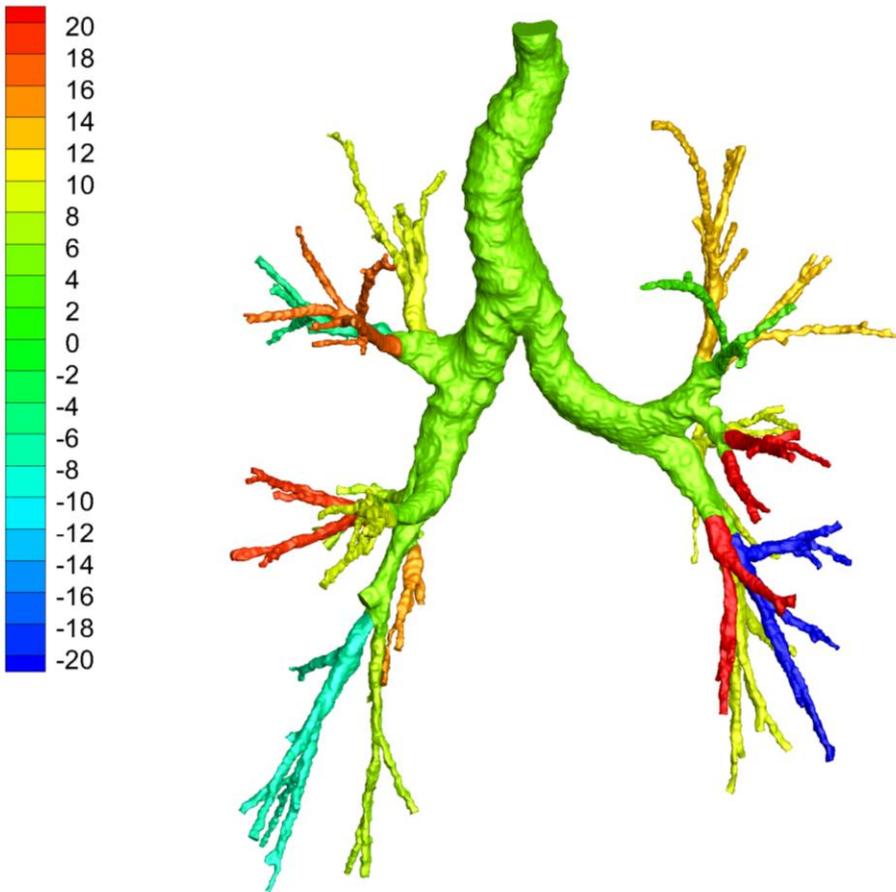


Figure 1 Changes in iVaw in a patient with a large response (FEV1 > 5%) to the Roflumilast treatment

iVaw changes [%] in Daxas® non-responder

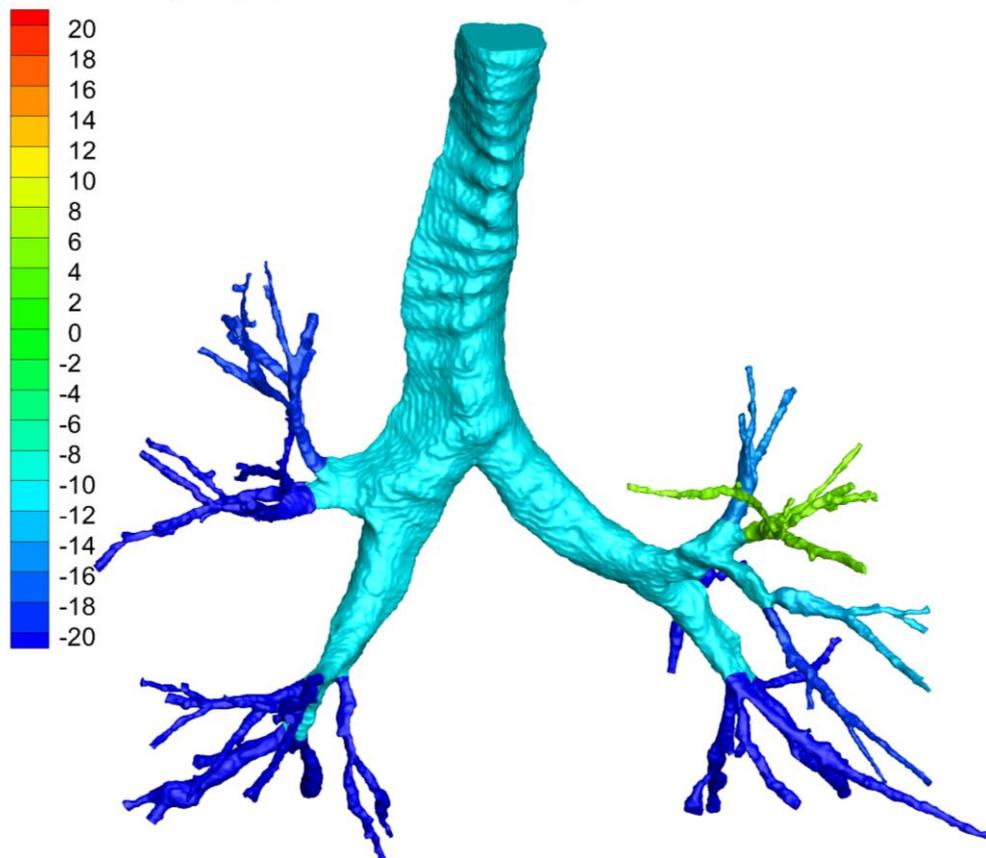


Figure 2 Changes in iVaw in a patient with no response ($FEV_1 > 5\%$) to the Roflumilast treatment