A double blind placebo controlled study to assess the effect of Roflumilast in addition to LABA/LAMA/ICS treatment in COPD patients using novel biomarkers.

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Background
Recently Roflumilast (Daxas®, Takeda) has been added as a therapeutic option for severe COPD patients. Roflumilast is a selective phosphodiesterase type 4 (PDE4). The current study 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 and a change in internal airflow distribution (IAD). The change in IAD enhances the deposition of the LABA/LAMA/ICS therapy leading to clinical improvements. Patients, who suffer from dynamic hyperinflation, tend to benefit from Roflumilast. These findings 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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Figure 1 Changes in iVaw in a patient with a large response (FEV1 > 5%) to the Rofumilast treatment
Figure 2 Changes in iVaw in a patient with no response (FEV1 > 5%) to the Roflumilast treatment