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Letter to the Editor

Effect of Roflumilast on Airway Blood Flow in COPD: A Pilot Study

Eliana S. Mendes, MD¹ Patricia Rebolledo, RT¹ Lilian Cadet, RT¹ Johana Arana, RT¹ Andreas Schmid, MD¹
Adam Wanner, MD¹

Abbreviations: airway blood flow, **Qaw**; chronic obstructive pulmonary disease, **COPD**; inhaled glucocorticoid, **ICS**; cyclic adenosine monophosphate, **cAMP**; phosphodiesterase-4, **PDE4**; forced expiratory volume in 1 second, **FEV₁**; long-acting beta2-agonist, **LABA**; long-acting antimuscarinic agent, **LAMA**

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¹ Division of Pulmonary, Allergy, Critical Care and Sleep Medicine, Department of Medicine, University of Miami, Miller School of Medicine, Miami, Florida

Address correspondence to:

Adam Wanner, MD
Email: awanner@miami.edu
Phone: (305) 243-3045

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To the Editor:

Inflammation typically is associated with changes in local vascular physiology including hyperperfusion. The airway circulation, derived from the systemic circulation, is no exception as shown in patients with asthma who have an increased airway blood flow (Qaw) that can be reversed with glucocorticosteroids through non-genomic and genomic mechanisms.¹ One could argue that the inflammatory increase in Qaw is a beneficial adaptation because it enhances the vascular clearance of locally released cytokines and other inflammatory mediators involved in the pathogenesis of airflow obstruction and mucus hypersecretion, features of asthma and chronic obstructive pulmonary disease (COPD). In contrast to asthma, airway blood flow is not increased in COPD.^{1,2} However, COPD is associated with airway vascular endothelial dysfunction as reflected by a blunted vasodilator response to inhaled albuterol.^{1,2} Therefore, pharmacologic restoration of beta2-adrenergic vasodilation could have therapeutic

benefits by virtue of increasing airway blood flow and the vascular clearance of inflammatory mediators, especially in acutely exacerbated COPD for which short-acting beta2-adrenergic rescue treatment is recommended.

In a previous study, long-term inhaled glucocorticoid (ICS) therapy only partially restored albuterol-induced vasodilation in the airway circulation of patients with COPD.¹ We wondered if the addition of the phosphodiesterase-4 (PDE4) inhibitor roflumilast to a COPD treatment regimen including an ICS could further enhance albuterol-induced vasodilation. Beta2-adrenergic receptor agonists including albuterol induce smooth muscle relaxation via cyclic adenosine monophosphate (cAMP). PDEs regulate cAMP, and it has been shown that PDE4 is expressed and degrades cAMP in airway smooth muscle.³ Since PDE4 is also expressed in vascular endothelium and smooth muscle,^{4,5} a PDE4 inhibitor would be expected to potentiate beta2-adrenergic agonist-induced vasodilation by inhibiting the degradation of cAMP, either indirectly by activating endothelial eNOS and generating NO, or by acting directly on vascular smooth muscle.^{6,7} In vitro observations tend to support this notion.^{3,8}

We therefore conducted a pilot study to test the hypothesis that in patients with COPD, long term treatment with the PDE4 inhibitor roflumilast restores albuterol-induced vasodilation in the airway as assessed by the measurement of Qaw, using a validated non-invasive gas uptake method that captures submucosal blood flow in airways defined by the anatomical dead space.⁹ We enrolled 11 patients with physician-

diagnosed COPD (Global initiative for chronic Obstructive Lung Disease stage ≥ 2)¹⁰ (Table 1). All were former smokers with a greater than 10 pack year smoking history and their screening day forced expiratory volume in 1 second (FEV₁) ranged between 38% and 65% of predicted with a <12% response to 180 μ g albuterol by inhalation. Their regular therapy consisted of an ICS, long-acting beta2-agonist (LABA) and long-acting antimuscarinic agent (LAMA), all of which were withheld on the experiment days. The vasodilator response to inhaled albuterol (180 μ g) was assessed by determining the change in Qaw as measured 15 min after drug inhalation (Δ Qaw). This was done before and after a 4-week treatment with roflumilast (500 μ g daily) or placebo as an add-on to regular therapy, using a double-blind cross-over design with an interceding 4-week washout period (4 experiment days). Multi-factorial analysis of variance was used to determine overall differences among treatments followed by a paired t-test to identify specific pair differences. Significance was accepted at $p < 0.05$.

On the 4 experiment days, mean (\pm SE) baseline Qaw values ranged between 45.9 ± 3.9 and $51.8 \pm 3.4 \mu\text{L} \cdot \text{min}^{-1} \cdot \text{mL}^{-1}$, where mL reflects the anatomic dead space ($p = \text{NS}$). While roflumilast treatment per se did not change Qaw significantly compared to placebo (56.3 ± 3.9 versus $60.7 \pm 3.7 \mu\text{L} \cdot \text{min}^{-1} \cdot \text{mL}^{-1}$; $p = \text{NS}$), it partially restored Δ Qaw (29.1 ± 6.8 versus $8.9 \pm 4.6\%$; $p < 0.05$). (Figure 1). In comparison, mean Δ Qaw was $50.1 \pm 8.3\%$ in age-matched healthy never smokers in a previous study.² The roflumilast effect was no longer seen after the washout period.

Mean (\pm SE) FEV₁ was $1.78 \pm 0.17\text{L}$ after placebo and $1.90 \pm 0.17\text{L}$ after roflumilast ($p = \text{NS}$). The subsequent responses to albuterol were $7.32 \pm 2.81\%$ and $5.81 \pm 2.82\%$, respectively ($p = \text{NS}$). This indicates that in this small group of patients on regular inhaler therapy, roflumilast by itself failed to increase FEV₁ significantly or to potentiate albuterol-induced bronchodilation. It appears that at least in COPD, the interaction between the PDE4 inhibitor roflumilast and the beta2-adrenergic agonist albuterol is stronger in airway vascular smooth muscle or endothelium than in airway smooth muscle. The observation is in keeping with in vitro studies showing a greater action of PDE4 inhibitors on beta2-adrenergic vascular smooth muscle relaxation than airway smooth muscle relaxation.^{11,12}

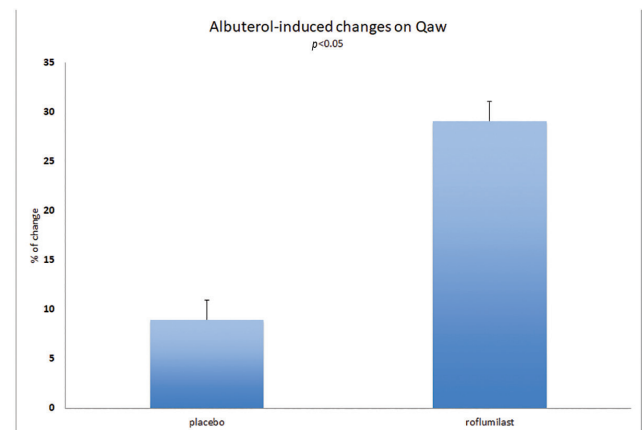
We conclude that a 4-week treatment with roflumilast partially restores albuterol-induced vasodilation in

Table 1. Patient Characteristics

N	11
Age (range), yr	61 ± 4 (53-74)
Sex (M/F)	9/2
Heart rate (bpm)	73 ± 12
Systolic BP (mmHg)	120 ± 13
Diastolic BP (mmHg)	74 ± 8
SaO₂ (mmHg)	95 ± 1
FEV₁ (% predicted)	54 ± 2
CO diffusing capacity (% predicted)	62 ± 5
Qaw ($\mu\text{L} \cdot \text{min}^{-1} \cdot \text{mL}^{-1}$)	45.9 ± 2.9

SaO₂=arterial blood oxygenation; Qaw=airway blood flow
Mean \pm SE

Figure 1. Acute Effect of Inhaled Albuterol on Airway Blood Flow



Acute effect of inhaled albuterol (180 μ g) on airway blood flow (Qaw) after adding placebo or roflumilast (400 μ g daily) for 4 weeks to regular COPD treatment. Qaw was measured before and 15min after albuterol administration. Mean \pm SE.

the airway of patients with stable COPD who have a blunted albuterol responsiveness despite the long-term combined use of an ICS, LABA and LAMA. By inference, this could be considered an anti-inflammatory effect of roflumilast by promoting albuterol-induced vascular clearance of inflammatory mediators from the airway, especially in acutely exacerbated COPD where albuterol is used as a rescue medication.

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