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Pulmonary hypertension therapy and COPD: still many questions to be answered

To the Editors:

After great development in the knowledge of pulmonary arterial hypertension (PAH) during the last decades, there is now an increasing interest in the pathophysiology of other forms of pulmonary hypertension, such as chronic obstructive pulmonary disease (COPD). The results obtained in the study by STOLZ *et al.* [1] have shown that for an average COPD Global Initiative for Chronic Obstructive Lung Disease stage III-IV population, the use of bosentan is not related to a significant improvement in exercise capacity and is associated with worsening of ventilation-perfusion mismatch. Although it is the first randomised study to address the use of bosentan, a proven PAH specific therapy, in the setting of COPD, the study design may lead to misinterpretation of the results. The study was not designed to treat COPD associated pulmonary hypertension. Furthermore, the absence of invasive measurements did not allow a proper subgroup analysis that could provide further support for the use of specific PAH therapy in the treatment of ''disproportional'' pulmonary hypertension associated with COPD. It is well known that most patients who present with pulmonary hypertension in the setting of COPD and other diseases actually have other associated causes for pulmonary hypertension development rather than an idiopathic PAH-like disease [2, 3], for instance, frequently presenting with some degree of left ventricle dysfunction. Since the study did not perform invasive haemodynamic assessment of the COPD patients, no assumption about a possible presence of post-capillary impairment, a situation in which bosentan has shown no effect so far [4], could be made.

Another matter of debate is the use of an echocardiogram to assess the presence of pulmonary hypertension in patients with severe COPD, since the technical difficulties in this specific clinical presentation have shown to impair the accuracy of this methodology.

In summary, we believe the authors have addressed an important question, but due to the chosen study design we remain with more questions than answers about the use of specific pulmonary arterial hypertension therapy in the setting of chronic obstructive pulmonary disease.

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STATEMENT OF INTEREST

None declared.

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To the Editors:

In the paper by STOLZ *et al.* [1], bosentan deteriorated not only exercise capacity but also hypoxaemia and quality of life among subjects with severe or very severe chronic obstructive pulmonary disease (COPD). While the concept of a new drug category which could improve functional status among these patients is challenging, the theoretical background and clinical data to support the rationale for this trial [1] is rather weak.

In the study by GUNTHER *et al.* [2], the use of bosentan in 12 subjects with idiopathic pulmonary fibrosis was generally well

tolerated and did not induce hypoxaemia in 12 weeks. However, there was a trend towards a decrease of forced vital capacity and diffusing capacity of the lung for carbon monoxide, while 6-min walking distance (6MWD) decreased from 320.9 m (232.96–408.84 m) to 302.9 m (205.01–400.79 m); $p<0.05$. Bosentan was not superior over the placebo in 6MWD in another double-blind, multicentre trial which included 158 patients with idiopathic pulmonary fibrosis [3]. Since the use of bosentan among patients with parenchymal lung disease has not proved to be favourable, the hypothesis that it could be beneficial for COPD subjects because they establish elevated levels of endothelin is rather weak.

While selective pulmonary vasodilation may benefit chronic obstructive pulmonary disease patients with increased pulmonary artery pressure during stress [4], this study was not designed to prove such an effect of bosentan. The pathophysiology of exercise limitation in severe chronic obstructive pulmonary disease subjects and the ventilation/perfusion ratio mismatching, which is induced by unselective pulmonary vasodilation [5], should have been taken more seriously under consideration in the study design of STOLZ *et al.* [1].

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STATEMENT OF INTEREST

None declared.

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To the Editors:

We read with interest the study by STOLZ *et al.* [1] reporting on the lack of improvement of exercise capacity caused by the dual endothelin-1 antagonist bosentan in patients with severe chronic obstructive pulmonary disease (COPD) and absence of severe pulmonary hypertension (PH) at rest. Pulmonary vasodilators, like bosentan or sildenafil, may not work in patients with COPD-related PH, a condition dominated by right ventricular diastolic dysfunction with normal cardiac output [2].

However, STOLZ *et al.* [1] acknowledged that these results may not apply to uncommon cases of severe PH associated with COPD. Thus it was suggested that PH-specific treatment first be studied in the subgroup of patients identified by CHAOUAT *et al.* [3], with severe disproportionate PH [4, 5], arbitrarily defined by a mean pulmonary arterial pressure ($\bar{P}_{pa}$) of >40 mmHg [3].

Herein, we report dramatic functional improvement with bosentan therapy in a patient with COPD and severe disproportionate PH. A 53-yr-old female with a history of obesity (body mass index 41 $kg \cdot m^{-2}$), type II diabetes, hypothyroidism and acute pulmonary embolism 3 yrs previously, was followed for severe COPD. She was a former smoker (30 pack-yrs) and her dyspnoea was functional class III. After two episodes of right cardiac failure 3 yrs previously she was receiving furosemide 80 $mg \cdot day^{-1}$. Obstructive sleep apnoea syndrome was ruled out. High-resolution computed tomography of the chest showed mild diffuse emphysema. Pulmonary function tests showed severe airflow obstruction with air trapping and hyperinflation: forced vital capacity (FVC) 2.3 L (76% predicted), total lung capacity 6.3 L (128% pred), forced expiratory volume in one second (FEV1) 0.84 L (34% pred), FEV1/FVC 37%, residual volume 4.0 L (226% pred) and carbon monoxide diffusion capacity was 87% pred. The patient had been on long-term oxygen therapy (2.5 $L \cdot min^{-1}$) for 3 yrs, with arterial oxygen tension (P_{a,O_2}) on long-term oxygen therapy of 11.0 kPa, but elevated carbon dioxide arterial tension (P_{a,CO_2}; table 1).

PH suggested by echocardiography was confirmed by right heart catheterisation, demonstrating a pulmonary artery pressure of 110/50 mmHg (mean 65 mmHg), with a transpulmonary gradient of 49 mmHg, cardiac index of 2.6 $L \cdot min^{-1} \cdot m^{-2}$ and pulmonary vascular resistance (PVR) of 739 $dyn \cdot s \cdot cm^{-5}$ without response to inhaled NO. No chronic thromboembolic disease or other cause of PH was found. The patient had not taken anorexigens and left ventricular function was normal. Since the contribution of PH to exercise limitation was considered significant and dyspnoea gradually increased, therapy with oral bosentan was initiated at 62.5 mg *b.i.d.* for 4 weeks, then increased to 125 mg *b.i.d.* Oral anticoagulation was initiated and long-term oxygen therapy was kept unchanged.

Within 4 weeks of bosentan initiation, dyspnoea significantly decreased to functional class II. The patient was able to resume activities such as home cleaning, going shopping and going to the beach. She could climb one flight of stairs without stopping (as opposed to no more than 5–10 steps before treatment) and resumed indoor biking. However, arterial blood gas analysis showed increased P_{a,CO_2} (9.6 kPa), and nocturnal noninvasive nasal ventilation was initiated 1 yr after the diagnosis of PH. Clinical improvement persisted throughout follow-up. Bosentan was well tolerated.

The 6-min walk test distance had improved from 198 to 360 m 2 yrs after initiating bosentan therapy. Right heart cavities