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Riociguat effectively treats chronic pulmonary hypertension

The investigational drug riociguat significantly improves markers for better outcomes in patients with inoperable or residual chronic thromboembolic pulmonary hypertension, according to results of the pivotal phase III CHEST-1 study.

CHEST-1 randomized 261 patients with inoperable chronic thromboembolic pulmonary hypertension or with persistent or recurrent pulmonary hypertension after surgery to 16 weeks' treatment with either oral riociguat daily or placebo. On the primary end point of change from baseline in 6-minute walking distance, riociguat resulted in an improvement of 46 metres (95% confidence interval 25–67 metres, $P<0.0001$) at 16 weeks compared to placebo.

Presenting the study in Atlanta, principal investigator Professor Ardeschir Ghofrani, Associate Professor of Internal Medicine, Department of Internal Medicine, Justus Liebig University, Giessen, Germany, said: 'CHEST-1 is the first positive phase III trial in chronic thromboembolic pulmonary hypertension. The 6-minute walking distance has been shown to be of value in the registration of drugs we currently have for pulmonary arterial hypertension. We have also seen that considerable changes on 6-minute walking distance reflect expected improvements in patient outcomes.'

Riociguat also resulted in significant improvements in secondary end points, including pulmonary vascular resistance, NT-proBNP, dyspnoea score, and quality of life scores. Treatment was well tolerated. The most frequent adverse events were headache, dizziness, peripheral oedema and gastrointestinal symptoms such as dyspepsia and nausea.

Professor Ardeschir Ghofrani, Associate Professor of Internal Medicine, Department of Internal Medicine, Justus Liebig University, Giessen, Germany

Chronic thromboembolic pulmonary hypertension is a life-threatening disease caused by thrombolic occlusion of the coronary vessels. Pulmonary endarterectomy is the standard of care and can be curable. However, the number of centres is limited worldwide – Papworth is the only UK centre to offer the intervention – and chronic thromboembolic pulmonary hypertension is sometimes inoperable. To date, no approved pharmacological therapies have been available for patients who cannot undergo surgery.

There were similarly positive data from PATENT-1, a phase III study in patients with pulmonary arterial hypertension, in which riociguat improved the 6-minute walking distance by a significant 36 metres (95% confidence interval 20–52 metres, $P<0.0001$) compared to placebo.

'These results, taken together with CHEST-1 results in chronic thromboembolic pulmonary hypertension, mean that riociguat is the first ever drug to demonstrate robust efficacy in two forms of pulmonary hypertension,' commented Professor Ghofrani.

The first of a new class of soluble guanylate cyclase stimulators, riociguat has a dual mode of action. It restores the nitric oxide–soluble guanylate cyclase–cGMP pathway, leading to increased generation of cGMP, important in regulating vascular tone, proliferation, fibrosis and inflammation. Submission of riociguat for regulatory approval in Europe and USA is expected in 2013.

Sue Lyon

Fewer exacerbations with roflumilast in severe COPD

Roflumilast reduces severe and moderate exacerbations in severe chronic obstructive pulmonary disease (COPD), according to a post-hoc pooled analysis of two multicentre clinical trials.

Presenting the data in Atlanta, Jason Yeaw, a health economist from IMS Consulting Group, California, USA, said: 'Overall, treatment with roflumilast led to a significantly lower rate of exacerbations, including in important clinical subgroups.'

The analysis included 1406 patients assigned to roflumilast and 1429 placebo patients. Compared with placebo, roflumilast significantly reduced the mean number of severe exacerbations per patient per year (0.17 *vs* 0.21, $P=0.0442$). This was seen in two of five study subgroups: patients with ≥2 prior exacerbations (0.25 *vs* 0.36, $P=0.0331$) and patients receiving a concomitant long-acting β2 agonist and ≥ 2 prior exacerbations (0.30 *vs* 0.46, $P=0.0395$).

The mean number of moderate exacerbations per patient per year was also significantly lower with roflumilast than with placebo (1.08 *vs* 1.32, $P<0.0001$). Exacerbations were reduced in all five subgroups: concomitant long-acting β2 agonist (1.13 *vs* 1.45, $P=0.0005$), concomitant long-acting muscarinic antagonist (1.38 *vs* 1.64, $P=0.0169$), ≥2 prior exacerbations (1.39 *vs* 1.79, $P=0.0028$), and concomitant long-acting β2 agonist and ≥2 prior exacerbations (1.34 *vs* 1.79, $P=0.0109$).

Roflumilast is a first-in-class, oral, once-daily phosphodiesterase type-4 inhibitor licensed for chronic obstructive pulmonary disease associated with chronic bronchitis as add-on to bronchodilator therapy. NICE recommends roflumilast only for patients with severe chronic obstructive pulmonary disease included in a clinical trial investigating the treatment in combination with a bronchodilator.

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