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TRIAL WATCH

Phase III success for first-in-class pulmonary hypertension drug

Data presented at the recent annual conference of the American College of Chest Physicians (ACCP) by Bayer for its oral soluble guanylyl cyclase (sGC) stimulator riociguat generated high hopes for the drug's potential in the treatment of pulmonary hypertension (PH). The primary end points were met in both of the pivotal Phase III studies, in which riociguat was evaluated in patients with pulmonary arterial hypertension (PAH) or in patients with inoperable or residual chronic thromboembolic pulmonary hypertension (CTEPH).

"Because of the unmet medical need for CTEPH, the excitement generated by the data from the CTEPH trial was particularly high," says Hossein A. Ghofrani, University Hospital Gießen and Justus-Liebig University, Germany, who was lead investigator on both trials.

CTEPH and PAH are subcategories of PH, in which different underlying mechanisms ultimately lead to right heart dysfunction. PAH is characterized by excessive vascular cell growth and inflammation, whereas CTEPH results from progressive occlusion of pulmonary vessels by recurrent emboli. Current therapies for PAH fall into three categories — endothelin receptor antagonists, prostacyclins and phosphodiesterase 5 (PDE5) inhibitors — which all aim to produce pulmonary vasodilatory actions. However, their efficacy decreases over time and a substantial number of patients do not respond to these therapies at all. Surgery by means of pulmonary endarterectomy is the treatment of choice for CTEPH but for the many patients who are inoperable or have no access to experienced surgical centres, no medical treatment exists. Consequently, new drugs are being sought for both indications, and sGC stimulators are one such option.

"The key role of the nitric oxide (NO)–sGC–cyclic GMP pathway in regulating pulmonary vascular tone is demonstrated by the findings that in various forms of PH, NO production and sGC activity are impaired while cGMP degradation is increased," says Oleg V. Evgenov, Massachusetts General Hospital, Harvard Medical School, Boston, USA, who has led preclinical research on sGC stimulators. "Stimulators of the sGC enzyme represent a novel class of compounds that increase cGMP production by directly targeting sGC to induce its activation via a dual mode of action. They stimulate sGC independently of NO owing to their distinct binding site on sGC, and they are also able to enhance sGC activity by sensitizing it to low levels of endogenous NO via stabilization of NO–sGC binding."

In the two trials, patients with PAH showed an improvement of 36 metres in the 6-minute-walk test (a standard outcome measure of improvement in exercise capacity) from the baseline after 12 weeks compared to placebo. Patients with CTEPH showed an improvement of 46 metres in the test from the baseline after 16 weeks compared to placebo.

The high interest generated by the trial results was not just due to the improvements in 6-minute walking time in both trials, but also due to the consistent results across the secondary end points in two distinct types of PH. "Besides PAH and CTEPH, riociguat also showed clinical effects in proof-of-concept studies in patients with PH secondary to left heart failure, interstitial lung disease and chronic obstructive pulmonary disease," says Evgenov. "Taken together, these promising results suggest that sGC stimulators may constitute a valuable new therapy approach for various groups of PH."

Nevertheless, "it would be too optimistic to say that riociguat would represent a cure [for PAH]; as with previous medications, in this trial there was no indication that patients had complete relief from the disease", says Ghofrani. "I would like to make an analogy to the oncology field, where rarely is there a magic bullet, or single drug, that tackles an underlying tumour: a polytherapy approach is needed."

Indeed, data also presented at the ACCP meeting indicated the potential of additional new PAH drugs in other classes; Actelion reported positive Phase III data for its novel dual endothelial receptor antagonist macitentan, which has been recently submitted to the US Food and Drug Administration for approval to treat PAH.

Man Tsuey Tse