Selexipag for inoperable CTEPH: why meeting a primary endpoint simply isn't enough

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Though this study met its primary endpoint and oral selexipag was approved as a treatment for inoperable CTEPH patients in Japan, the overall results and scope of this study do not justify a valid position for selexipag in the treatment armamentarium. https://bit.ly/3INAYgO

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In the current issue of the *European Respiratory Journal*, Ogo *et al.* [1] report the results of a randomised, placebo-controlled, multicentre trial (RCT) from Japan, in which the effects of selexipag in patients with inoperable chronic thromboembolic pulmonary hypertension (CTEPH) were investigated. All patients had previously been treated by either surgery (*i.e.* pulmonary endarterectomy; PEA) or intervention (*i.e.* balloon pulmonary angioplasty; BPA) [2], and were suffering from persistent or recurrent pulmonary hypertension. The primary objective of the trial was the change in pulmonary vascular resistance (PVR). In fact, PVR was significantly reduced; however, the effect was at best moderate, and notably many relevant secondary endpoints, such as the 6-min walking distance (6MWD), serum N-terminal pro-brain natriuretic peptide (NT-proBNP), and World Health Organization functional class did not change in a meaningful manner. The adverse events profile corroborated the known side-effect profile of selexipag, as previously reported from trials in the field of pulmonary arterial hypertension (PAH). Based on the results of this study, selexipag was approved for patients with inoperable CTEPH in Japan.

In light of the unimpressive haemodynamic response, the lack of beneficial changes in many secondary endpoints, a rather small-scaled trial with a relatively high drop-out rate, and the availability of other effective medical therapies for these patients, the results of this study should be critically discussed. Analogies can be drawn from PAH, for which many agents are approved which therapeutically impact three well described pathways (*i.e.* the endothelin, prostacyclin, and nitric oxide/soluble guanylate cyclase (sGC)/cyclic guanosine monophosphate pathways) [3]. In this therapeutic area we learned over the past years that, while costly, combinations of complementary drugs from the above-mentioned pathways are the mainstay of therapy for PAH patients. Even more so, upfront or early combinations of drugs are recommended, as they have proven to be very efficacious in reducing PVR by up to 50%, alongside with improvements in clinical endpoints. In this context, selexipag was investigated in an event driven RCT (GRIPHON study) [4], in which an impressive relative risk reduction of 40% was shown in favour of selexipag to reduce the occurrence of clinical events. However, other secondary endpoints only showed marginal improvements: for example, 6MWD changed by only 12 m after 26 weeks, New York Heart Association functional class did not improve and moderate changes were observed for NT-proBNP. Alongside the negative outcome of the TRITON study [5], in which a triple-upfront combination therapy with selexipag plus an endothelin receptor antagonist (ERA) and a phosphodiesterase 5 inhibitor was not superior to a dual combination therapy with the latter two, there is ample evidence showing that selexipag is a marginally effective, but rather side-effect rich, treatment.

In the field of CTEPH, the endothelin receptor antagonist bosentan, for many years a cornerstone of PAH therapy, was tested in patients with inoperable disease (in the BENEFIT study) [6]. However, while PVR, one of two co-primary endpoints in this trial, was significantly reduced by 24.1%, exercise capacity did

not change, and thus the study results did not fulfil criteria to grant registration. This drawback halted the exploration of other medical therapies for years, based on the notion that if bosentan cannot help these patients, no targeted medical therapy will. This assumption, however, changed substantially when the results of the CHEST-1 study, a positive pivotal RCT investigating the effects of the sGC stimulator riociguat, were published [7]. Riociguat reduced PVR by more than 30% and improved 6MWD by 46 m and, accordingly, became the first approved therapy for inoperable CTEPH patients. Since then, other PAH approved medications have been investigated as potential CTEPH therapeutics, amongst which subcutaneous treprostinil also was granted an indication, based on the results of the CTREPH study (reduction of PVR by 17%, improvement in 6MWD of 41 m) [8]. In the MERIT study, macitentan, another ERA, showed promise in a phase-II RCT, as it reduced PVR by 16% and improved 6MWD by 34 m [9], and is currently investigated in a pivotal phase-III RCT with a daily dose of 75 mg. We should, however, keep in mind that with regards to the patient populations included (*e.g.* with or without pulmonary hypertension-specific medication, post-surgical persistent or recurrent pulmonary hypertension, pre-inclusion operability assessment) a lot of heterogeneity exists between the aforementioned studies, and therefore direct comparisons should be interpreted with caution.

In addition to the above listed evidence, over the past few years, interventional therapy by means of BPA has become an important treatment option for patients with inoperable CTEPH. Moreover, the best strategies are currently under investigation to answer the question whether medical treatment prior to BPA is recommended.

Focusing on the present study by Ogo *et al.* [1], we should acknowledge the positive outcome of the study, but also shed some light on the relevance of the overall findings for patients. First, the sample size of this study is rather small. Consequently, more than 10% missing data are likely to influence the results of the study. Second, the efficacy of selexipag, as assessed by its ability to lower PVR can be interpreted, at best, as modest. Lastly, the lack of changes in most of the clinically relevant secondary endpoints is disappointing. Except for a trend to improvement in NT-proBNP, the other parameters did not show notable changes. Patients with pulmonary hypertension rightfully expect both relief of symptoms, improved quality of life and better functionality, all of which are hardly to be expected with selexipag in light of the current results.

More research will be needed to finally address the role of oral selexipag as a potential therapy for patients with inoperable CTEPH. An ongoing randomised controlled trial, the SELECT study, will ultimately inform us about selexipag's utility. In the meantime, the richness of choices, including approved medications, intervention by means of BPA and, most importantly, surgical therapy by PEA, already provides a highly effective multi-modal treatment armamentarium for our patients with CTEPH.

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