Pulmonary Hypertension Update

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Pulmonary arterial hypertension (PAH) and chronic thromboembolic pulmonary hypertension (CTEPH) are progressive diseases of the pulmonary circulation that lead to right heart failure. Exciting recent advances have improved prognosis, however PAH and CTEPH remain disabling and life limiting conditions.

Currently approved medical therapies improve functional capacity, hemodynamics and delay clinical worsening by targeting the 3 main pathobiologic pathways: prostacyclin, endothelin, and nitric oxide. Recently, several new agents targeting the classic PAH pathways have been developed for the treatment of pulmonary hypertension. However, a targeted treatment that delays or reverses vascular remodeling remains elusive. Recent attempts to specifically inhibit or reverse vascular proliferation in PAH with imatinib, a tyrosine kinase inhibitor, were disappointing as more than 30% of patients discontinued due to adverse events.

Selexipag is a new oral selective PGI2 receptor agonist that targets the prostacyclin pathway. In the GRIPHON study of 1156 patients with PAH, selexipag reduced the risk of death or complications related to PAH by 40%, an effect that was primarily driven by a reduction in disease progression and hospitalization for PAH, not mortality. Importantly though, the treatment effect was consistent across treatment of naïve patients and those receiving background phosphodiesterase type 5 (PDE5) inhibitors and/or endothelin receptor antagonists. Unlike PDE5 inhibitors, riociguat acts by directly stimulating soluble guanylate cyclase, independent of nitric oxide availability. In recently published long-term extension studies of PAH patients and CTEPH patients, riociguat was well tolerated with sustained improvements in functional capacity and 6-minute walk distance. Riociguat is also the only targeted medication currently approved for treating CTEPH.

Combination therapy in PAH has gained momentum; however, there remains some debate on the optimal strategy: upfront versus sequential addition of therapies. The COMPASS-2 study evaluated a strategy of sequentially adding bosentan to patients on background sildenafil for at least 12 weeks. This was a negative study with regards to the primary endpoint; however, a long recruitment period and high dropout resulted in the study being underpowered. In contrast, the AMBITION trial evaluated an upfront combination approach using ambrisentan and tadalafil versus monotherapy in treatment naïve patients. There was a 50% reduction in the primary endpoint with initial combination therapy, driven by a reduction in hospitalization for PAH. Based on the results of AMBITION, initial combination therapy with ambrisentan and tadalafil was given a class IB recommendation in the recent European guidelines. This recommendation is supported by a recent analysis showing a 3-year survival of 84% with initial dual oral combination therapy compared to an expected historical 3-year survival of 66%.

Balloon pulmonary angioplasty (BPA) has emerged as an exciting alternative treatment option for patients with non-operable CTEPH. The first series from 2001 demonstrated a reduction in mean pulmonary artery pressure (mPAP) of 9 mmHg, but reported a 5.6% rate of death. With refinements in technique, several reports now support the efficacy and safety of BPA. The hemodynamic benefits were summarized in a recent review article, with an overall reduction in mPAP of 12-21 mmHg from baseline, and a mortality rate of 0.0-3.4% after 2-5 angioplasty sessions. Sustained hemodynamic improvements, almost to within the normal range, have been reported up to 3.5 years after BPA. Severe and fatal complications, including reperfusion edema or pulmonary artery perforation, may be minimized with accumulation of experience. Although the indications and limitations have not been fully established, BPA has the potential to become a key treatment strategy for patients with non-operable CTEPH.
References


