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Pulmonary arterial hypertension: available treatments in the modern era

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ABSTRACT

The several randomized controlled trials (RCTs) conducted in the last 25 years in the field of pulmonary arterial hypertension (PAH) have led to the approval of over 10 drugs, which seek to restore the right balance between vasoconstrictor and vasodilator factors, and to the consequent increase of the median survival. However, no medical treatment is currently curative. Ongoing research is focusing on how to preserve right ventricle (RV) function, curbing the inexorable progression of the disease towards right heart failure and death. Below, we provide a comprehensive review of the current available PAH specific therapies and briefly report the therapeutic strategies adopted by PH specialists in clinical practice.

Pulmonary arterial hypertension (PAH) is a rare and progressive syndrome characterized by the remodeling of small pulmonary arterial vessels and the consequent increase of pulmonary vascular resistance (PVR). In the earlier stages of the disease, the right ventricle (RV) improves RV-to-pulmonary artery coupling and preserves cardiac output undergoing hypertrophic changes; in the later stages, homeometric adaptation fails, RV volumes increase and consequently the left ventricle underfills, finally leading to heart failure [1].

Despite the significant increase of the median survival achieved over the years, the war against PAH is not won yet: no medical treatment is currently curative; thus, clinicians efforts are aimed at curbing the inexorable progression of the disease towards right heart failure and death and at preserving RV function, the main prognostic determinant.

Thanks to several randomized controlled trials (RCTs) conducted in the last 25 years in this field, more than 10 drugs have been approved for the treatment of PAH. Targeting the three signaling pathways involved in the pathogenesis of the disease (the prostacyclin, the endothelin and the nitric oxide), they try to re-establish the right balance between vasoconstrictor and vasodilator factors.

Below, we summarize the specific drugs currently available for the management of PAH patients and briefly report the treatment algorithm adopted by PH specialists in clinical practice.

ENDOTHELIN RECEPTOR ANTAGONISTS (ERAs)

The ERAs antagonize the effect of endothelin (ET), a potent pulmonary vasoconstrictor mainly secreted by the vascular endothelial cells, whose plasma and lung levels are increased in PAH patients. The ET-1 effects are mediated by two receptor subtypes: the type A (ET_A), expressed on pulmonary smooth muscle cells, causes vasoconstriction; whereas the type B (ET_B), predominantly localized on the vascular endothelium, promotes the release of nitric oxide (NO) inducing vasodilatation.

The three oral ERAs approved for PAH treatment are bosentan, macitentan and ambrisentan, the latter the only ET_A selective.

Sitaxentan, initially authorized in 2006, on December 2010 was worldwide withdrawn from the market due to several cases of fatal idiosyncratic hepatotoxicity.

As resulted from multicenter placebo-controlled trials (the BREATHE-1, the ARIES and the SERAPHIN), ERAs improve pulmonary hemodynamics, exercise capacity, functional class (FC) and clinical outcomes [2-4].

They can cause peripheral edema, due to systemic vasodilatation; elevation in serum aminotransferase concentration, due to a transient and reversible transaminitis, and anemia. Being teratogenic, they should not be used during pregnancy.

PHOSPODIESTERASE-5 INHIBITORS (PDE-5i)

In PAH patients there is an upregulation of the type 5 isoform of cyclic nucleotide phosphodiesterase (PDE-5), the enzyme that catalyzes the conversion of cyclic guanosine monophosphate (cGMP) to GMP. Inhibiting the degradation of the second messenger of NO, the PDE-5 inhibitors cause vasodilatation and reduce cell proliferation. As shown by the SUPER and the PHIRST trials, sildenafil and tadalafil, included in this group of agents, significantly improved 6MWD, NYHA FC and hemodynamics in PAH patients [5-6].

Headache, flushing and dyspepsia are the most common side effects reported with their use.

SOLUBLE GUANYLATE CYCLASE STIMULATOR (sGC)

PDE5-I are not effective in all PAH patients, likely due to the reduced NO production typically observed in the disease. These patients with insufficient response to PDE5-I therapy may benefit from the switch to riociguat, a first-in-class soluble guanylate cyclase stimulator characterized by a dual mode of action within the NO-sGC pathway: it induces vasorelaxation and antiproliferative effects both sensitizing the sGC to endogenous NO and directly stimulating the enzyme through a different binding site, independently of NO availability [7].

In PATENT-1 trial, riociguat significantly improved the 6MWD, the PVR, the WHO FC, the NT-proBNP and the time to clinical worsening in PAH patients treatment naïve or pretreated with ERAs or prostanoids [8]. The improvements in exercise capacity and functional class were maintained in the long-term as resulted from the PATENT-2 open-label extension study [9].

The next open label studies, RESPITE and REPLACE, supported the switching to riociguat as an effective strategy to improve clinical outcomes, in PAH patients not at treatment goal despite PDE5-I therapy, combined or not with ERA [10-11].

Riociguat is contraindicated in pregnancy and, due to the unfavourable safety profile and the lack of a positive benefit/risk ratio reported in the PATENT PLUS study [12], cannot be combined to PDE-5i. Dizziness, dyspepsia and headache have been the most common adverse events related to its use.

PROSTANOIDS AND SELECTIVE NON-PROSTANOID PROSTACYCLIN RECEPTOR (IP) AGONISTS

Prostanoids, including epoprostenol, treprostinil and iloprost, are still the mainstay in the treatment of PAH pa-

tients, thanks to their several effects (vasodilatory, antiproliferative, anti-inflammatory and anti-platelet) mediated by the G-protein-coupled prostanoid IP receptors.

Epoprostenol, a synthetic analogue of prostacyclin, was the first therapy approved for PAH patients in 1995, basing on data of two RTCs showing its significant positive effects on exercise capacity, pulmonary hemodynamics and survival, compared to conventional therapy [13].

Due to the short plasma half-life (<3-5 min), epoprostenol requires a continuous intravenous infusion through a central venous catheter and a portable infusion pump. Patients education and care in the self-management of this complex delivery system are pivotal to avoid serious complications, as infection and thrombosis of the catheter.

Nausea, vomiting, headache, hypotension and flushing are the most common side adverse effects reported with epoprostenol use, often limiting its up titration.

In contrast to epoprostenol, treprostinil, the next prostacyclin analogue FDA approved for PAH patients, has a longer half-life (4-6 h) and a less cumbersome delivery system: it can be administered subcutaneously (s.c.) through a small self-inserted s.c. catheter, usually changed every 2-4 weeks, and a mini-infusion pump. In a 12-week double-blind randomized, placebo-controlled trial, enrolling 470 PAH patients, treprostinil showed to improve exercise capacity, hemodynamics parameters, quality of life and indices of dyspnea with several advantages over epoprostenol [14].

Treprostinil can cause diarrhea, jaw pain, flushing and infusion site pain, that could be minimized using oral analgesics or topical cold and hot packs.

To overcome the serious drawbacks and the significant burden associated with external pump delivery systems, in carefully selected cases clinicians can choose other therapeutic options to act on the prostacyclin pathway:

1. **Iloprost**, a chemically stable prostacyclin analogue typically administered by inhalation. The specific nebulisers used for its delivery produce small aerosolized particles, thus ensuring alveolar deposition, selective pulmonary vasodilatation and less systemic adverse effects. However, despite the improvements in exercise capacity, NYHA FC and clinical deterioration reported with its long-term administration, the use of inhaled iloprost in clinical practice is limited by the high number of daily inhalations (six to nine) and the prolonged inhalation times. Modern vibrating mesh nebulizers, recently developed, could overcome these drawbacks, increasing patient's acceptance and adherence to therapy [15].
2. **Oral prostanoids**.
   - Beraprost, having similar pharmacologic properties to epoprostenol but a longer half-life, improved exercise capacity and symptoms in NYHA FC II and III PAH patients enrolled in the ALPHABET study [16] but in the next 12-month trial didn't show to maintain the positive effect on exercise endurance in the long term [17]. Currently beraprost is approved for the treatment of PAH only in Japan and South Korea.
   - Oral treprostinil has been approved by FDA in 2013 after three large multicenter RTCs. In contrast to the FREEDOM-C and the FREEDOM-C2 studies not reaching statistical significance in the primary endpoint of 6MWD, the next FREEDOM-M conducted in treatment-naïve PAH patients showed improvement in the exercise capacity in the oral treprostinil group. The last trial, the FREEDOM-EV, showed the effect of oral treprostinil in reducing the clinical worsening when added in PAH patients who recently started specific oral monotherapy [18-21].
3. **Selective non-prostanoid prostacyclin receptor (IP) agonists**. Binding the prostacyclin receptors (IP) expressed on platelets, smooth cells and endothelial cells, they promote vasodilatation and inhibit platelet aggregation and smooth cell proliferation. To date, only selexipag has received FDA approval for the treatment of PAH patients thanks to the GRIPHON trial results, showing its significant positive effects on the primary composite end point of death from any cause or a complication related to PAH [22].

Ralinepag, the other selective IP agonist, has shown to significantly reduce PVR compared with placebo in a phase 2 study enrolling 61 PAH patients treated with mono or dual combination background therapy; however, the phase 3 trial, ADVANCE OUTCOMES, evaluating its impact on time to clinical worsening and on exercise capacity is still ongoing [23].

Headache, nausea and diarrhea are the most common adverse events reported in patients treated with these drugs.

4. **Lenus pro** ®, an implantable pump, has been recently developed for the continuous intravenous infusion of treprostinil. The system, usually located in subcostal area, releases the drug solution into superior caval vein through a tunnelized catheter inserted via subclavian vein and needs a percutaneous refill every 28 days. Short-term studies are promising, mainly in terms of patients' satisfaction and improvements in quality of life, but further studies are needed to test the effects of this new implantable pump on traditional outcome measures [24].

TREATMENT ALGORITHM FOR PAH PATIENTS

The main goals of PAH therapy are the improvement of RV function and the achievement of a low-risk status, assessed by different multiparametric risk scores (e.g. ESC/ERS PH guidelines risk table and REVEAL score).

Until a few years ago, a sequential combination strategy was recommended for incident PAH patients: they were initially treated with one oral drug and then re-evaluated after 4-6 months to add another class of drug when the predefined therapeutic goal was not reached.

Later on, the publication of the AMBITION trial results [25] marked an important turning point in the PAH therapeutic algorithm, with the recommendation of an upfront combination therapy (start of two types of drugs at the same time after the diagnosis).

Indeed, as widely demonstrated by the most recent literature, acting simultaneously on different PAH pathogenetic pathways, upfront combination therapy provides more pronounced improvements on pulmonary hemodynamic, RV volumes and function compared with oral monotherapy. Particularly, the most significant results in terms of hemodynamic status improvement are achieved when the initial dual combination therapy includes a parenteral prostanoid plus a single oral therapy (mPAP reduction of 9-29% and PVR reduction of 35-56%).

Ongoing studies are even focusing on the potential role of an initial triple combination therapy that includes a parenteral prostanoid, reporting its striking results on PVR and mPAP reduction (by around 70% and 30% respectively). However, experience is still limited to recommend this aggressive therapeutic strategy in clinical practice.

Following the recommendations proposed during the 6th World Symposium on PH, we can briefly summarize the current PAH treatment algorithm as follows [26]:

- patients responders to the acute vasoreactivity testing during the right heart catheterization (decrease of mean PAP of at least 10 mmHg from baseline, with a drop of mean PAP below 40 mmHg and no decrease in cardiac output compared to baseline after NO inhalation) should be treated with high doses of calcium channel blockers. These patients should be re-evaluated after 3-6 months to identify those with inadequate response needing the starting of PAH specific medications.
- Non-responders patients at low or intermediate risk should be treated with an upfront oral combination therapy including an ERA and a PDE5-i.
- Non responders patients at high risk should be treated with an initial combination therapy including an intravenous prostanoid.

  A multidisciplinary re-evaluation within 3-6 months allows to identify patients needing the escalation to triple combination therapy and, in most advanced cases, the referral for lung transplantation.

CONCLUSION

Despite the improvements achieved in the last 25 years, PAH is still an incurable disease. The most powerful therapies are also the most aggressive ones. Thus, careful patients selection for parenteral prostanoids, adequate titration of specific drugs, regular risk stratification and valid psychological support are the key points for the therapeutic success and the achievement of treatment goals.

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