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LEADING ARTICLE

Improving Survival in Patients with Pulmonary Arterial Hypertension: Focus on Intravenous Epoprostenol

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Abstract

Pulmonary arterial hypertension represents a devastating disease, causing progressive increase of pulmonary vascular resistance leading to right ventricular dysfunction and death. Therapeutic management has rapidly advanced in recent years due to improved understanding of pathophysiology and new drugs have been developed; however, survival remains poor. Oral agents as phosphodiesterase type V inhibitors, the soluble guanylyl cyclase stimulator riociguat, the prostacyclin receptor agonist selexipag and the endothelin receptor antagonists have each achieved evidence-based validation and are recommended for pulmonary arterial hypertension. Initial oral monotherapy or combination therapy is recommended for patients with low or intermediate risk according to each patient's risk stratification. Intravenous epoprostenol is a synthetic prostacyclin and the first drug approved for the disease. Although it represents the only treatment shown to reduce mortality, it is underused. Survival rates for patients treated with oral combination drug therapies are lower than those for patients treated with initial combination therapies including intravenous epoprostenol. This raises the interesting question of whether intermediate risk pulmonary arterial hypertension patients should be routinely introduced to therapies including intravenous epoprostenol rather than combination oral therapies.

Key Points

Initial oral combination therapy with specific pulmonary arterial hypertension drugs is the appropriate strategy for low risk patients.

Intravenous epoprostenol in combination with oral drug therapies must be considered as appropriate strategy for intermediate risk patients and remains the mainstream approach for those in high risk.

Comprehensive patient assessment and risk stratification in expert pulmonary hypertension centers is important to guide treatment decisions and to monitor disease progression.

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1 Survival of Pulmonary Arterial Hypertension Patients Treated with Specific Drugs

Survival of pulmonary arterial hypertension (PAH) patients has improved in the last two decades, however, it remains suboptimal. According to the "Registry to Evaluate Early and Long-Term PAH Disease Management" (REVEAL), a 55-center observational US registry of PAH patients, the 5-year survival for previously diagnosed patients was 65.4% compared to 61.2% for newly diagnosed patients [1]. Additionally, patients who improved from functional class (FC) World Health Organization (WHO) III to I/II, either newly or previously diagnosed and regardless of PAH cause, had better survival vs patients who remained in FC III [2]. Prior to the development of PAH-specific drug therapies, the median survival rate in the first published registry, in 1991, studying newly diagnosed patients with idiopathic PAH was 2.8 years, with survival rates of 68%, 48%, and 34% at 1,3, and 5 years, respectively [3].

A REVEAL registry analysis of utmost importance [1] demonstrated that previous diagnosed patients, classified as FC WHO IV at enrollment having previous exposure in drug therapies, were nonresponsive or less responsive to therapy. In contrast, newly diagnosed patients classified

FC IV at enrollment representing a treatment-naïve population, had greater opportunity to improve with specific drug therapy. This analysis demonstrated that the single point-in time measurement of FC represents an important predictor of survival in patients with PAH, despite its inherent limitations, but also that the initial therapeutic approach plays significant role in our patients' outcome, preventing the disease progression.

2 Current Treatment Strategy According to Risk Stratification

To improve patients' outcomes, treatment goals of pulmonary hypertension (PH) were proposed at the 5th World Symposium on PH held in Nice, France in 2013, leading to risk stratification according to parameters proved to be associated with better survival. According to 2015 European Society of Cardiology and European Respiratory Society guidelines for the diagnosis and treatment of PH [4], risk stratification provides an estimate for individual patients' annual mortality risk. Patients can be classified in low, intermediate or high risk (annual mortality lower than 5%, between 5 and 10% or over 10% respectively). Risk stratification must be performed at baseline and during regular follow up (every 3–6 months). Most of the proposed variables and cut-off values are based on expert opinion. The recommendations suggest a comprehensive assessment and the achievement of a low risk profile patient should be the main treatment goal. Right heart catheterization and right ventricular function studies are mandatory, as are closely related to patient's outcome. Regular follow-up is necessary, with escalation of therapies if warranted, aiming at a low risk profile, improvement of overall quality of life and better outcome.

The recommended risk stratification has recently been evaluated by studies from 3 European registries [5–7], which consistently demonstrated that a low-risk profile confers a survival advantage compared with other risk categories. Conversely, deterioration in risk category is associated with worse outcomes. A relationship between disease progression and increased risk of death is intuitive and has been observed in clinical practice [8]. Moreover, it is supported by a retrospective analysis of data from the REVEAL registry [9] which reported that clinical worsening events are prognostic of subsequent mortality. Of note, hospitalizations are not yet included in current stratification, representing a substantial omission. Underlying factors such as age and comorbidities play an additional significant role, but there are not mentioned in current risk stratification and the individual criteria are not weighted according to their relative importance, for example in case of scleroderma-induced PAH.

The use of multiple variables used for risk stratification causes complexity. Good clinical judgement is necessary as patients are likely to have several variables indicative of low risk, and some of intermediate or high risk. Furthermore, the potential for inter-clinical variation is increased, especially in the current era, where guidelines propose the use of multiple different drugs and treatment strategies.

3 Pulmonary Arterial Hypertension Oral Drug Therapy and mortality data

3.1 Active Treatment with Oral Drugs vs Placebo and Sequential Combination Therapy

In the pharmacotherapeutic management of PAH, the efficacy of phosphodiesterase type V inhibitors (PDE-5) as tadalafil [10] and sildenafil [11], the soluble guanylyl cyclase stimulator riociguat [12], and endothelin type A and type B receptor antagonists (ERAs) bosentan [13–16] and ambrisentan [17] have each achieved evidence-based validation as specific drug therapy in PAH. The primary composite endpoint (EP) in trials through which these oral drugs are approved, was 6-minute walk distance (6MWD) and there was no impact of mortality reduction. In a meta-analysis by Manes et al. [18], the overall mortality reduction with active specific drug therapy was shown to be 18% ($p = 0.51$). Meta-analysis of published randomized controlled studies in PAH in 2010 has included 3780 patients of 23 trials. An overall reduction of mortality of 44% ($P = 0.016$) was shown for patients in active treatment groups when compared with control groups [19]. Meta-analysis of published randomized controlled studies in PAH by Galie et al. [20] demonstrated that sequential combination therapy provides a superior clinical benefit compared to patients treated with monotherapy.

The SERAPHIN [21] and GRIPHON [22] trials documented that in stable patients in FC WHO II or III, the sequential combination therapy with macitentan (ERA) in patients already receiving a PDE-5 and with selexipag (prostacyclin IP receptor agonist) as add-on therapy in patients already treated with ERA or PDE-5 or both, respectively, reduced the primary composite EP of morbidity and mortality compared with placebo, predominantly via reduction in hospitalization. Reduction in hospitalization is proved to be related with a better survival in PAH patients [23], but these two trials do not give us any evidence of mortality reduction. The impact of morbidity in these two trials on the risk of subsequent mortality was assessed by McLaughlin et al. [24]. On the basis of the 3-month landmark time point, patients who experienced a morbidity event before month 3 had an increased risk of death compared with patients who did not. The hazard ratios [HR] in the SERAPHIN and in the GRIPHON study were 3.39 (95% confidence interval [CI]: 1.94 to 5.92) and 4.48 (95% CI: 2.98 to 6.73), respectively. Analyses based on 6-month and 12-month landmarks also

showed increased risk in patients who experienced morbidity events, albeit with a reduced HR. So, this study demonstrates the prognostic relevance of PAH-related morbidity, highlighting the importance of preventing disease progression. However, the percentage of patients with death as the EP at the end of SERAPHIN and GRIPHON trials was 14.5% for the macitentan 10 mg group vs 17,6% for placebo with a HR 0.77 (0.46–1.28), $p = 0.25$ and 17.4% for selexipag group vs 18% for placebo with a HR 0.97 (0.74–1.28), ($p = 0.42$), respectively. Death as primary EP in these studies was 6.6% for macitentan group vs 6.8% for placebo group in SERAPHIN, and 4.9% for selexipag group vs 3.1% for placebo group in the GRIPHON study.

3.2 Initial Combination Oral Drug Therapy Versus Initial Monotherapy

Combination therapy targeting multiple pathophysiological pathways is considered the standard of care in PAH. AMBITION trial [25] paved the way for the initial combination therapy, as the time for clinical failure for combination group patients was significantly reduced compared to each of the two monotherapy groups. The percentage of patients with death as the EP at the end of AMBITION study was 8% for the combination therapy vs 11% for the pooled monotherapy with a HR 0.72 (0.4–1.27), ($p = 0.25$). Death as primary EP was presented in 4% for the combination therapy group vs 3% for pooled monotherapy group. Initial combination therapy was also associated with a decrease in the hazard for the primary EP by 79% ($p = 0.005$) among patients with FC WHO II status, indicating the benefit for this strategy in mildly symptomatic patients.

A post-hoc analysis of AMBITION trial [26] demonstrated that at the end of the study, 10% of combination therapy group patients died, compared to 14% of monotherapy group patients with a 33% mortality risk reduction (HR 0.67; 95% CI 0.42–1.08; $p = 0.10$). Average follow-up was 101 weeks in the combination group and 94 weeks in the pooled monotherapy group. However, at the end of treatment, which was specified as the period until the end of the randomized treatment plus seven days, 1% of combination therapy group patients died compared to 4% of monotherapy group patients, with a mortality risk reduction of 79% (HR 0.21; 95% CI 0.06–0.73; $p = 0.0065$). The average time until the end of treatment on study drug was 96 weeks for combination therapy and 91 weeks for the pooled monotherapy group. These data put forward the hypothesis that initial combination therapy can be associated with better long-term survival than initial monotherapy.

In a retrospective analysis of real-world clinical data [27], Sitbon et al. explored the effect of different combinations of first-line PAH specific dual oral therapy with an ERA plus a PDE5 inhibitor on hemodynamic parameters and clinical and functional outcomes in newly diagnosed PAH patients. Overall survival rates were 97%, 94% and 83% at 1, 2 and 3 years, respectively. Expected survival rates calculated from the French equation for these patients were 86%, 75% and 66% at 1, 2 and 3 years, respectively. Reductions in PVR were significant with all treatment regimens and exceeded 40%.

4 Intravenous Epoprostenol in Pulmonary Arterial Hypertension

Epoprostenol was the first drug approved for PAH, with a worldwide experience combined and with a wide array of data supporting its efficacy profile. It causes immediate vasodilatation of pulmonary and systemic vessels, resulting in long-term hemodynamic improvement by significant Pulmonary Vascular Resistance (PVR) reduction (Table 1). In PAH, normal release of endogenous prostacyclin is diminished. Epoprostenol represents a synthetic prostacyclin which activates EP3 and IP pathway, promotes intracellular cyclic AMP production and inhibits thromboxane A2 production and the calcium influx into cells, causing powerful vasodilation, and attenuation of vascular smooth cell proliferation [38]. The current guidelines for the diagnosis and treatment of PH [4] outline the remaining role of epoprostenol for PAH patients in FC WHO III and IV as monotherapy or upfront combination therapy alongside oral drugs.

A key RCT reported a significant decrease in total PVR after a short period of time of intravenous epoprostenol, during 8 weeks of therapy, with maintenance of the hemodynamic improvement over 18 months [29]. Barst et al. [30] showed in a trial of 81 pts with idiopathic PAH receiving epoprostenol, a significant reduction of PVR and mean pulmonary arterial pressure (mPAP), as well as a better quality of life. Similar hemodynamic and clinical improvements have been shown at a trial with PAH in 111 scleroderma patients [39]. BREATH-2 study [40] was a 16-week assessment of epoprostenol alone or in combination with bosentan in 33 PAH patients. Combination therapy was associated with a 36.3% reduction of total PVR compared to a 22.6% reduction in the monotherapy group (p: 0.08). Sitbon et al. analyzed patients treated with epoprostenol, ERA and PDE-5 [35], without control group, who had spectacular improvement pulmonary hemodynamics. All patients with upfront triple combination therapy (epoprostenol included), were still alive after an average follow up of 41.2 ± 13.4 months. Overall survival estimates were 100%, 100% and 100% at 1, 2 and 3 years, and respective transplant-free survival estimates were 94%, 94% and 94%. Expected survival calculated from the French equation was 75% (95% CI 68–82%), 60% (95% CI 50–70%) and 49% (95% CI 38–60%) at 1, 2 and 3 years, respectively.

Table 1 Key studies in PAH patients with haemodynamic improvement, according to pulmonary vascular resistance reduction and survival improvement

Study (first author, year, ref)	Study design	Treatment	PVR changes-key outcomes
Rubin [28]	Exploratory	EPO	PVR decrease > 20%
Rubin [29]	RCT	EPO	PVR decrease > 40%
Barst [30]	RCT	EPO	PVR decrease > 21%
Shapiro [31]	Single-center	EPO	PVR decrease by 21%
McLaughlin [32]	Observational	EPO	3-y S.R. 62.8%
Sitbon [33]	Observational	EPO	3-y S.R. 63%
Bergot [34]	Observational	EPO	3-y S.R. 88%
Sitbon [35]	Retrospective	Initial EPO+ ERA + PDE5	3-y S.R. 100%
Ogawa [36]	Retrospective	EPO + ERA + PDE5	3-y, 10-y S.R. 96%, 78%
Ogawa [37]	Retrospective	EPO + ERA + PDE5	3-y, 10-y S.R. 92%, 69%

EPO epoprostenol, *ERA* endothelin receptor antagonist, *PDE5* phosphodiesterase V inhibitor, *PVR* pulmonary vascular resistance, *RCT* randomized controlled trial, *S.R.* survival rate, *Y* year

Kemp et al. studied [41] retrospectively PAH patients in FC WHO III and IV from the French registry after they had received a first-line combination therapy with Bosentan and epoprostenol, and interestingly, their overall survival estimation was 100%, 94%, 94% and 74% at 1, 2, 3 and 4 year period. The transplant-free survival estimates were 96%, 85%, 77% and 60% respectively.

From the observational French pulmonary hypertension registry study (2006-2010), after just 4 months of epoprostenol therapy, both PAH-specific treatment-naïve and PAH-specific treatment-allocated patients saw significant improvement. The greatest survival benefit was in treatment-naïve patients treated with upfront combination of epoprostenol plus oral drug therapy with a 1- and 3 year survival at 92% and 88% respectively [34]. Analysis of Japanese patients from 3 PH centers from 1992 to 2012 with an average survival time from treatment initiation 14.7 ± 0.8 years (95% confidence interval, 13.1 to 16.3 years), showed 1-, 3-, 5-, and 10-year survival rates 97.9%, 92.1%, 85.8%, and 69.5%, respectively [42]. In a study [37] conducted by Ogawa et al. intravenous epoprostenol was highly prescribed, especially for FC WHO III patients. The mean survival time from diagnosis was 14.9 ± 0.8 years (95% CI, 13.4–16.4 years), with 1-, 2-, 3-, 5- and 10-year survival rates of 98, 96, 96, 96 and 78%, respectively. Hemodynamic parameters improved significantly with treatment, despite severe compromise at baseline.

The significant improvement in survival for patients treated with intravenous epoprostenol is attributed to PVR and mPAP reduction. Dosage seems to have a crucial role in patient's hemodynamic improvement, but no standard dosing regimens have been proposed. The recommended dose is 25–40 ng/kg/min [38]. Ogawa et al. reported [37] an average dose of 80 ng/kg/min, with 5-year survival rate of 96% and a substantial reduction of mean PAP and PVR, by 44% and 67% respectively. Akagi et al. [43] studied a high-dose epoprostenol dosage in sixteen consecutive patients with idiopathic PAH. The mean dose was 107 ± 40 ng/kg/min (range 54–190 ng/kg/min) and the mean duration of high-dose epoprostenol therapy was 1.355 ± 627 days (range 582–2.410 days). Significant decreases from baseline values were seen in mPAP (from 66 ± 16 to 47 ± 12 mmHg, $p < 0.001$) and PVR (from 21.6 ± 8.3 to 6.9 ± 2.9 Wood units, $p < 0.001$). Compared with the baseline state, high-dose epoprostenol therapy reduced mPAP by 30% and PVR by 68%. Tokunaga et al. [42] have also reported that a rapid uptitration of epoprostenol soon after initiation, was associated with a continuous decrease in mPAP and better survival compared to slow uptitration. The rapid increase group received epoprostenol at a dose higher than 20 ng/kg/min at 3 months and more than 45 ng/kg/min at one year of treatment. The rapid increase group was associated with a continuous reduction in mPAP during the follow-up period, whereas the slow increase group showed no reduction in mPAP after 6 months of treatment. The 9.5-year survival rate was also significantly better in the rapid increase group compared with the slow increase group (100% vs. 64%, $p = 0.022$). We believe that the minimum dose achieved at three months of treatment should be 20 ng/kg/min with a goal at the maximum tolerated dose, avoiding a high cardiac output state.

Treatment with epoprostenol is associated with dose-related adverse events during initiation and dose escalation, most commonly jaw pain, headache, nausea, vomiting, headache, hypotension and flushing [44]. Other adverse events, including infection and thromboembolic events, are typically related to the central venous catheter drug-delivery route. Antithrombotic therapy is necessary and catheter-related infections can be minimized through adherence to standard practices of safe treatment administration, such as protocols

for sterile drug preparation and local practice protocols for intravenous drug administration [45, 46].

Other prostacyclin analogues as inhaled iloprost are recommended for patients in FC WHO III, but long-term studies were conducted in prevalent PAH patients and have shown inconsistent results [47]. A recently published study [48] of 267 PAH patients from an observational Spanish registry treated with inhaled iloprost, showed a 3-year survival rate of 54%, despite clinical improvements, with a high discontinuation rate of 75%. Treprostinil in subcutaneous and inhalational formulations are recommended as an option for initial treatment of patients in WHO FC III and may be considered in WHO FC IV. The indication of subcutaneous treptostinil is based on a 12 weeks RCT which resulted in small but significant improvement in 6MWD vs placebo [49]. Infusion site pain was the most common adverse effect of treprostinil, leading to discontinuation of the treatment in 8% of patients. An RCT with intravenous treprostinil in PAH patients was performed but the enrolment of this trial was terminated due to safety considerations, after the randomization of 36% of the planned patients (126 patients) [50]. A recent study [51] of long-term outcomes of patients of intravenous treprostinil administered via the implantable LENUS Pro pump in patients with severe PH showed an overall survival rate at 1, 2, and 3 years of 85.3%, 76.2%, and 66.5% respectively. However, it should be noted that serious adverse events were related to complications due to the pump.

5 Conclusions

PAH remains an incurable disease despite the available therapeutic options and survival improvement is unsatisfactory. In 1982, median survival for IPAH was only 2.8 years [3], whereas it now exceeds 7 years in the US REVEAL registry [52]. The original National Institutes of Health registry included mainly HPAH and IPAH, 64% of patients had incident disease and the 1- and 3-year mortality rates were 68% and 48%, respectively [3]. In 2010, 298 prevalent and 56 incident cases of IPAH, HPAH, and anorexigen associated PAH were followed up for 3 years in the French network on pulmonary hypertension [53]. In that study, 76% of patients were prescribed PAH-specific therapy, and the 1- and 3-year survival rates were 85.7% and 54.9%, respectively.

Intravenous Epo remains the only drug providing a mortality benefit in PAH. Nevertheless, it's challenging mode of administration results at least in a delay of its use, as many patients who need it, have never been treated with it. Farber et al. investigated the aggressiveness of therapy in patients enrolled in the REVEAL registry who deteriorated to FC IV or died. Among patients with PAH-related mortality or all-cause mortality, only 56% (n = 272 of 487) and 43% (n = 391 of 908) respectively were receiving intravenous prostacyclin [54].

Survival rates for patients treated with oral combination drug therapies are lower than those for patients treated with initial combination therapies including intravenous epoprostenol. This raises the interesting question of whether PAH patients should be started routinely on therapies including intravenous epoprostenol rather than combination oral therapies. Since head-to-head comparisons among different treatment strategies using intravenous epoprostenol are not available, no evidence-based first-line therapy with initial combination therapy with Epo can be proposed.

Hypothetically, if epoprostenol were the only drug we had at our disposal, survival would be better for our patients. But how can we secure a more effective use of the available drugs for incident patients with PAH?

Epoprostenol is mandatory for high-risk patients. For patients with an intermediate risk profile, classified in FC WHO III associated with impaired right ventricular function, epoprostenol could be used as first line therapy in combination with oral agents. Initial dual or triple oral combination therapy (including selexipag) may be an alternative strategy, but a close follow-up is essential. Near-normal hemodynamic profile in six months should be the goal of treatment, but if this goal is not achieved, epoprostenol should be considered the necessary drug to be added in the oral combination drug therapy. Initial oral combination therapy is considered the standard of care and should be applied in low risk patients. Initial monotherapy may remain the option for a minority of low risk patients not included so far in the oral combination trials, for example patients with HIV disease or portal hypertension.

Time is life for patients with PAH and we are obliged to apply the most appropriate therapeutic approach according to the best evidence-based data we have. Not all physicians are experienced in the initiation and long-term use of epoprostenol, which probably plays a significant role in its underuse in clinical practice. Additionally, initial combination therapy has the potential to be associated with practical challenges and additive side effects [55]. Specialist healthcare professionals in PAH-centers with expertise and experience in therapeutic management of PAH patients is mandatory.

Compliance with Ethical Standards

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