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Review

Management of Pulmonary Arterial Hypertension Patients with World Health Organization Functional Class II

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Pulmonary arterial hypertension (PAH) is an incurable chronic and progressive debilitating disease associated with significant morbidity and mortality. The World Health Organization functional class (WHO FC) at diagnosis and at follow-up remains one of the strongest predictors of survival in PAH. Studies have shown improved long-term outcomes in PAH patients who received PAH-specific treatment, as monotherapy or as combination therapy, early in their disease course. Studies have also shown that without treatment, PAH rapidly deteriorates even in patients with less advanced (low risk) disease state.

In this article, we review evidence from randomized controlled clinical trials to support our position on the importance of early PAH management in WHO FC II patients. The growing importance of combination therapy in the early treatment of PAH and recommendations by the most recent guidelines for the diagnosis and treatment of pulmonary hypertension are also discussed in this article.

Key Words: Early treatment • Pulmonary artery hypertension • World Health Organization Functional Class

INTRODUCTION

Pulmonary arterial hypertension (PAH) is a progressive disease associated with intimal proliferation and fibrosis, medial hypertrophy, and adventitial thickening in the distal small pulmonary arteries (< 500 μm in diameter).[1,2] As PAH progresses, arterial remodeling also becomes severe with formation of plexiform lesions, which is difficult, if not impossible, to reverse even with cessation of the insult and initiation of PAH treatment.[3] Arterial remodeling can be attenuated,[4] ameliorated and even reversed in the absence of plexiform lesions.[5] As such, it is important to treat PAH early in its course. The clinical staging of PAH is classified according to World Health Organization functional assessment classification (WHO FC), which was itself modified from New York Heart Association Functional Classification.[1,6] WHO FC grading is based on patient assessment, from WHO FC I in which the patient does not experience dyspnea or fatigue, chest pain, or near syncope during ordinary physical activity, to WHO FC IV in which the patient is unable to carry out any physical activity without experiencing symptoms.[1,6] Early PAH clinical trials mainly included patients in later stages of disease (i.e. WHO FC III/IV).[7-11] However, with the publication of the EARLY trial in 2008, more and more studies have shown that patients with less severe disease (i.e. WHO FC II) benefit

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Table 1. A summary of publications discussing treatment effects on WHO FC II PAH

Reference	Main study	Main findings
Galie (2008)[12]	EARLY	• PVR decreased and six-minute walk distance increased vs. placebo • 77% risk reduction in time to clinical worsening vs. placebo
Simonneau (2014)[26]	EARLY	• At 4 years, event-free survival at 80%, and survival at 85% which are improvements compared to historical data
Souza (2013)[25]	SERAPHIN	• At month 6, patients who maintained at WHO FC II have fewer PAH-related death or hospitalizations vs. those at WHO FC III
Channick (2014)[27]	SERAPHIN	• Lesser proportion of WHO FC I/II patients experienced mortality/morbidity events vs. those in WHO FC III/IV in those who received macitentan on top of their baseline therapy
Galie (2017)[28]	SERAPHIN	• At month 6, patient who were WHO FC I/II at baseline showed numerically better improvements in hemodynamics than those who were WHO FC III/IV at baseline
Chin (2019)[30]	GRIPHON	• Selexipag has a more pronounced treatment benefit in patients with low NTproBNP levels at baseline vs. those at higher levels
Coghlan (2018)[32]	GRIPHON	• 64% risk reduction in mortality/morbidity in WHO FC II patients vs. 26% risk reduction in WHO FC III patients when selexipag is added to baseline therapy
Frost (2015)[31]	AMBITION	• 79% risk reduction in time to first clinical failure in WHO FC II patients vs. 42% in WHO FC III patients who received combination therapy with ambrisentan and tadalafil

FC, functional classification; NTproBNP, N-terminal pro-brain natriuretic peptide; PAH, pulmonary arterial hypertension; PVR, pulmonary vascular resistance; WHO, World Health Organization.

from PAH-specific therapies.[12-16] These studies (see Table 1) led to various guidelines recommending monotherapy or initial combination therapy for patients with low-risk status, the majority of whom are in WHO FC I/II.[2,17-18]

RATIONALE FOR EARLY TREATMENT OF PAH

Although WHO FC II patients are only mildly symptomatic, their lung vasculature already shows advanced pathological changes, and their right ventricle shows structural and functional changes.[19,20] As a result, WHO FC II patients still experience disease progression when left untreated or if they receive insufficient treatment, as demonstrated in the EARLY, SERAPHIN, GRIPHON, and AMBITION trials.[12-14,16]

Historically, WHO FC at diagnosis or at follow-up has been considered to be the strongest predictor of survival in PAH patients.[21-23] The REVEAL registry indicated that WHO FC II PAH patients had better 5-year survival than WHO FC III PAH patients (75.6% vs. 57.0%, respectively).[24] In the SERAPHIN trial, PAH patients who deteriorated from WHO FC II to III/IV had an almost four-fold increase in the risk of PAH-related death or hospitalization [hazard ratio (HR) 3.71, 95% confidence interval (CI) 1.67-8.25; p = 0.001].[25]

Taken together, we believe that the stage at which a patient is diagnosed and treated is very important and supports the rationale for initiating PAH treatment early in the disease course to prevent rapid worsening and its associated poor prognosis.

IMPACT OF EARLY PAH MANAGEMENT: EVIDENCE FROM RANDOMIZED CONTROLLED TRIALS

The EARLY trial was a randomized, placebo-controlled trial investigating the efficacy and safety of bosentan in mildly symptomatic patients.[12] Prior to the EARLY trial, there were no dedicated placebo-controlled studies exclusively in WHO FC II PAH patients. The EARLY trial demonstrated that in WHO FC II PAH patients, bosentan, when compared to placebo, significantly reduced pulmonary vascular resistance [pulmonary vascular resistance (PVR), 83.2% vs. 107.5% of baseline value, treatment effect -22.6%, p < 0.0001] and increased 6-minute walk distance (6MWD, 11.2 m vs. -7.9 m from baseline, mean treatment effect 19.1 m, p = 0.0758).[12] Long-term data from the EARLY open label extension phase showed, after a median exposure to bosentan of 51.4 months, that the majority of patients maintained (77.8%) or improved (17.1%) their WHO FC.[26]

The SERAPHIN trial, the first long-term morbidity and mortality study completed in PAH, enrolled 742 patients, 52.4% of whom were in WHO FC II.[13] The SERAPHIN trial showed that macitentan 10 mg significantly reduced the risk of time to first morbidity or mortality event by 45% compared with placebo ($p < 0.001$).[13] An analysis of SERAPHIN data showed that, at month 6, patients in WHO FC II at baseline experienced less PAH-related death or hospitalization compared to those who were in WHO FC III at baseline (independent of which treatment arm the patients were randomized to).[25] Further, a pre-specified analysis of SERAPHIN data showed that macitentan 10 mg improved the long-term outcomes of PAH patients compared with placebo, by significantly and consistently reducing the risk of morbidity and mortality and death or hospitalization due to PAH, irrespective of WHO FC at baseline (p-values of interaction, 0.64 and 0.60, respectively); with WHO FC I/II patients showing numerically fewer events compared with WHO FC III/IV patients.[27] In a hemodynamic sub-study of SERAPHIN, macitentan showed consistent improvements in PVR (-44.7% in WHO FC I/II and -32.6% in WHO FC III/IV) and cardiac index (CI, +0.69 L/min/m^2 in WHO FC I/II and +0.58 L/min/m^2 in WHO FC III/IV) at month 6 regardless of baseline WHO FC.[28]

The beneficial effects of starting treatment early rather than later were also seen in the GRIPHON trial, the first completed randomized controlled trial in PAH which allowed triple combination therapy.[14] In the GRIPHON trial, 46% of 1,156 patients enrolled were in WHO FC II.[14] The GRIPHON trial found that selexipag reduced the risk of time to first morbidity or mortality event by 40% compared with placebo ($p < 0.001$), and this efficacy was consistent across baseline WHO FC subgroups (p-value of interaction, 0.78).[14] Exploratory analysis of GRIPHON data using a subpopulation treatment effect pattern plot (STEPP) showed a more pronounced treatment effect of selexipag versus placebo in patients treated earlier compared to those treated later (HR for risk of morbidity or mortality at 0.45 vs. 0.70, respectively).[29] Based on risk level stratified according to baseline N-terminal pro-brain natriuretic peptide (NTproBNP) level, post-hoc analysis of GRIPHON data showed that the risk of time to first morbidity or mortality event was 92% lower in selexipag-treated patients with a low NTproBNP level (less likely to be in WHO FC III/IV), and 90% lower in the placebo-treated group, in comparison to patients with a high NTproBNP level (patients tended to be in higher WHO FC).[30]

Taken together, these data suggest that intensifying treatment in WHO FC II is associated with a more pronounced treatment effect compared to WHO FC III. It is possible that patients in WHO FC II respond better to interventions due to less severe pulmonary arterial remodeling than those in WHO FC III.

COMBINATION THERAPY IN EARLY PAH MANAGEMENT

Since achieving and maintaining low-risk status, which in the past was equated with achieving and maintaining WHO FC II, is the accepted treatment goal, there is now more emphasis on starting combination therapy, either upfront or sequential, earlier in PAH management (e.g. WHO FC II).[2,17,18]

Considering the cost of treatment, sequential combination therapy is the most utilized treatment strategy in PAH and is often considered to be the standard of care. Rapid escalation of therapy is recommended to achieve treatment goals and maintain or reestablish low-risk status.[2,17,18]

Upfront combination with an endothelin receptor antagonist (ERA) and a phosphodiesterase type 5 inhibitor (PDE-5i) is recommended for WHO FC II patients[2,17,18] based on the AMBITION trial which showed that initial combination therapy with ambrisentan and tadalafil reduced the risk of clinical failure by 50% in newly diagnosed, treatment naïve PAH patients compared with pooled monotherapy.[16] Subgroup analysis of the AMBITION data showed significant risk reduction in the time to first clinical failure event in WHO FC II and III patients [79% ($p = 0.0052$) and 42% ($p = 0.0062$), respectively] with combination therapy compared to pooled monotherapy.[31]

In the GRIPHON study, 376 patients received background therapy with ERA and PDE-5i, 115 of whom were in WHO FC II at baseline.[32] The group in which selexipag was added (triple therapy) showed a 37% reduction in the risk of time to first mortality or morbidity event compared with the placebo group (dual therapy) (HR 0.63; 95% CI 0.44-0.90), consistent with the overall study population.[32] In patients who were in WHO FC II at base-

line, the one-year Kaplan-Meier event-free survival estimates (95% CI) were 93.3% (80.6-97.8) and 79.3% (65.7-88.0) for triple and dual therapy, respectively; the estimates for WHO FC III patients were 79.5% (70.2-86.1) and 70.1% (61.1-77.4) for triple and dual therapy, respectively.[32] There was a reduction of 64% in morbidity and mortality risk in WHO FC II patients compared to 26% in WHO FC III patients.[32]

These data support the use of combination therapy in patients with early stage PAH (WHO FC II). There are currently no data to support starting treatment earlier than WHO FC II. In addition, there is currently insufficient evidence to support starting treatment in patients with mean pulmonary arterial pressure (mPAP) > 20 mmHg, the revised PAH hemodynamic definitions proposed during the 6th World Symposium on Pulmonary Hypertension.[33]

GUIDELINE RECOMMENDATIONS

Guidelines recommend the use of multiple parameters to assess the long-term prognosis and guide treatment plan for patients with PAH.[2,17,18] WHO FC is an important prognostic factor and is part of the multiparametric risk assessment recommended by guidelines.[2,17,18] The goal of PAH treatment is to achieve and maintain patients at a stable low risk status to achieve the best possible outcomes.[2,17,18] In order to achieve this, the guidelines highlight the importance and provided evidence-based recommendations to initiate PAH-specific therapy early in the disease course (WHO FC II) to delay disease progression.[2,17,18] To ensure that the patients remain in a low risk status, it is very important that frequent, regular, and systematic assessments are conducted every 3 to 6 months, to catch patients who may need early escalation of therapy.[2,17,18]

CONCLUSION

PAH remains a progressive disease, and although some will live for decades, others are not that fortunate and will experience sudden deterioration and die. Mortality risk is still seen in WHO FC II patients. Therefore, early interventions are of the utmost importance to improve long-term outcomes. Substantial evidence shows that patients in lower risk status also benefit from treatment. Guidelines recommend maintaining patients in a low risk status to improve long-term outcomes. Currently, no treatments can reverse pulmonary vasculature with plexiform lesions (late-stage changes); therefore, we should improve early diagnosis to catch patients who are still in a pathologically-reversible state and optimize our treatment strategies in the hope of reversing and preventing disease progression to achieve long-term disease control in our PAH patients. Further studies are warranted to investigate whether starting treatment at WHO FC I or at a lower mPAP can reverse pathological changes.

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CONFLICTS OF INTEREST

All authors declare no conflicts of interest.

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