ASK THE EXPERT

How Might Adherence to the Treatment Recommendations of the 2013 Fifth World Symposium on Pulmonary Hypertension Improve Long-Term Outcomes?

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A significant expansion in knowledge regarding the diagnosis and treatment of pulmonary arterial hypertension (PAH) within the past 2 decades has transformed a very high-mortality disease without specific therapy for the majority of patients to one with 10 drugs as very effective therapeutic choices.[1] Yet despite these advances, data from various worldwide registries indicate a sobering 5-year survival between 21% and 68%.[2] While ongoing pulmonary vascular research holds the promise of future novel treatment modalities for PAH,[3] the more immediate impact of the Fifth World Symposium on Pulmonary Hypertension (WSPH) on disease treatment may be the intensifying focus on goal-oriented therapy.[4]

Whether the term is "goal-oriented therapy," "treat-to-target strategies," or "goal-directed therapy," the treatment approach to PAH is evolving in a manner similar to that of other diseases such as diabetes and sepsis. The treat-to-target trial, published in 2003,[5] reported the results of using different insulin types added to oral diabetic therapy as a combination treatment approach in meeting a specific target hemoglobin A_{1c}. The results demonstrated that insulin could be safely added to oral therapy, more effectively achieving the recommended targets of diabetes care. In 2001, when an acceptable treatment goal for PAH may have been any functional improvement or even disease stability, an approach to early goal-directed therapy for severe sepsis and septic shock was published.[6] This sepsis treatment algorithm monitored cardiovascular parameters including central venous pressure, mean arterial pressure, and mixed venous oxygenation, and responded with directed therapies to meet specific goals. The goal-directed therapy group had nearly half the mortality due to sudden cardiovascular collapse compared with the standard-therapy group in that trial. Both of these studies contain parallels to evolving PAH care: the diabetes trial for its promulgation of an earlier combination therapeutic approach to improve care, and the sepsis trial for its use of well-established treatments to achieve goals and not relying on a newly developed drug or device in their algorithm. The diabetes trial, however, benefited from a single, well-accepted marker of disease treatment in the hemoglobin A_{1c}, while the sepsis trial may be more relevant to PAH as it relied on a combination of cardiovascular parameters to describe its treatment targets.

Defining a set of treatment targets for guiding PAH therapy was becoming established by 2005[7] with the publication of Hoeper and colleagues, who described their clinical practice of progressive therapeutic interventions aimed at achieving a 6-minute walk distance greater than 380 meters, peak oxygen uptake during exercise testing of greater than 10.4 mL/min/kg, and peak systolic blood pressure greater than 120 mm Hg during exercise. These authors observed a significant improvement in actual survival compared to expected survival and that of historical controls, as well as reduced requirement for initiation of intravenous prostacyclin and referral for lung transplantation. Subsequently, in 2010, Sitbon and Galiè reviewed additional prognostic data in PAH and stressed the importance of using multiple goals to assess the adequacy of response to therapy in individual patients.[8] The European Society of Cardiology/European Respiratory Society guidelines for pulmonary hypertension[9] are cited in that review, which (similarly to the American College of Cardiology/American Heart Association 2009 expert consensus document on pulmonary hypertension)[10] recommend clinical evidence of right ventricular (RV) failure, rate of symptom progression, syncope, World Health Organization functional class, B-type natriuretic peptide (BNP)/N-terminal BNP, echocardiographic findings, and hemodynamics as additional determinants of prognosis to incorporate when assessing treatment strategies.

The Fifth WSPH report on treatment goals of pulmonary hypertension builds on these previous guidelines and appropriately promotes identification of clinically relevant treatment goals that correlate with long-term outcome as a top priority.[4] While incorporating previously defined treatment goals, the WSPH report also emphasizes our evolving approach to set more aggressive

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Table 1. Clinically relevant, goal-oriented parameters to determine response to therapy and prognosis in patients with PAH according to the Fifth WSPH guidelines
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- Functional class I or II
- Normal/near normal RV size and function
- Hemodynamics: Normalization of RV function defined as RAP <8 mm Hg, CI >2.5 to 3 L/min/m^2
- 6-minute walk distance >380 to 440 m; this goal may not be aggressive enough for younger individuals
- Peak oxygen uptake (VO_2) >15 mL/min/kg and $EqCO_2$ <45 L/min/M
- Normal B-type natriuretic peptide level

Abbreviations: $EqCO_2$=ventilatory equivalent for carbon dioxide; CI=cardiac index; RAP=right atrial pressure; RV=right ventricle

targets for patients to achieve in terms of exercise capacity and right heart function, as these are known to be important correlates of long-term outcome (Table 1). Right heart function as assessed by cardiac magnetic resonance imaging and echocardiographic parameters other than estimated RV systolic pressure, such as tricuspid annular plane systolic excursion (TAPSE), RV strain, RV area, and pericardial effusion expand on those cardiac parameters emphasized in previous publications. Importantly, this workforce on treatment goals also reaffirmed that published studies have consistently shown that composite treatment goals are more predictive of long-term outcomes than any single test.

In summary, our overall aim of maximizing survival and function in PAH may best be achieved by utilizing a goal-oriented approach in clinical practice, as was shown to significantly benefit outcomes in illnesses such as diabetes and sepsis. Unlike diabetes, however, PAH clinicians must utilize a multifaceted assessment, as in PAH we are lacking a single reliable test equivalent to the hemoglobin A_{1c}. We need to rely on composite treatment targets, which have proven successful in the early goal-directed treatment of sepsis. Ultimately, we realize that our patients face multiple challenges during their journey with PAH. If we pursue the updated PAH treatment algorithm as our roadmap for optimal use of currently available therapy,[11] then the goal-oriented parameters for follow-up assessment may serve as our signposts to help keep our patients on course.

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