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Clinical Worsening as Composite Study End Point in Pediatric Pulmonary Arterial Hypertension

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BACKGROUND: Clinical worsening (CW), an increasingly used composite end point in adult pulmonary arterial hypertension (PAH), has not yet been evaluated in pediatric PAH. This study aims to evaluate the usefulness of CW in pediatric PAH by assessing the event incidence and prognostic value of each separate component of CW and of the composite CW end point.

METHODS: Seventy pediatric patients with PAH from the Dutch National Network for Pediatric Pulmonary Hypertension, who started PAH-targeted therapy between January 2000 and January 2014, were included in the study and underwent standardized follow-up. The following CW components were prospectively registered: death, lung transplantation (LTx), PAH-related hospitalizations, initiation of IV prostanoids, and functional deterioration (World Health Organization functional-class deterioration, $\geq$15% decrease in 6-min walk distance, or both). The longitudinal event incidence and prognostic value were assessed for each separate component and their combination.

RESULTS: The end-point components of death, LTx, hospitalizations, initiation of IV prostanoids, and functional deterioration occurred with a longitudinal event rate of 10.1, 2.5, 21.4, 9.4 and 48.1 events per 100 person-years, respectively. The composite CW end point occurred 91.5 times per 100 person-years. The occurrences of either hospitalization, initiation of IV prostanoids, or functional deterioration were predictive of death or LTx ($P < .001$ for each component). In this cohort, 1-, 3-, and 5-year transplant-free survival was 76%, 64%, and 56%, respectively. Freedom from CW at 1, 3, and 5 years was 43%, 22%, and 17%, respectively.

CONCLUSIONS: CW occurred with a high event incidence and each of the soft end-point components was predictive of death or LTx. This supports the usefulness of CW as a study end point in clinical trials in pediatric PAH. CHEST 2015; 148(3):655-666

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ABBREVIATIONS: 6MWD = 6-min walk distance; APAH-CHD = pulmonary arterial hypertension associated with congenital heart disease; APAH-non-CHD = pulmonary arterial hypertension associated with conditions other than congenital heart disease; CW = clinical worsening; HPAH = heritable pulmonary arterial hypertension; IPAH = idiopathic pulmonary arterial hypertension; IQR = interquartile range; LTx = lung transplantation; PAH = pulmonary arterial hypertension; REVEAL Registry = Registry to Evaluate Early and Long-term PAH Disease Management; WHO-FC = World Health Organization functional class

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Pediatric pulmonary arterial hypertension (PAH) is a severe, progressive disease of the pulmonary vasculature and has an unsatisfactory prognosis despite the introduction of PAH-targeted therapies.[1-3] Most drugs currently used in the treatment of PAH have not been evaluated in pediatric clinical trials.[4,5] This is largely explained by the rarity and heterogeneity of pediatric PAH, leading to small study cohorts, but is also due to the lack of appropriate outcome parameters to evaluate drug efficacy.[6-8]

Time to death would seem the most robust trial end point, as improving survival is the first priority in treating pediatric PAH.[3] However, death as an end point would require long-duration clinical trials in a very vulnerable group of pediatric patients unable to give consent, thereby challenging study ethics and leading to high costs.[7,8] Short-duration clinical trials with lower numbers of patients required are preferable but need an alternative end point to obtain sufficient statistical power. Such an end point should be either a direct or surrogate measure of how a patient feels, functions, or survives[9] and would ideally be able to be measured earlier and more frequently than the final end point of interest.[10] Such an end point would lead to increased statistical power, reduction of required study participants, shorter study periods, and lower costs.[11]

The 6-min walk distance (6MWD) has been the most commonly used primary end point in the pivotal trials in adult PAH.[12,13] The absolute value of 6MWD is regarded as a clinically meaningful end point, measuring how a patient functions. Moreover, 6MWD has been demonstrated to be an independent predictor of mortality in adults and in children >7 years old.[14,15] However, in the current era with accumulating treatment modalities, more ambitious treatment effects such as improved morbidity and mortality are desired. Evidence suggests that changes in 6MWD are not accurate surrogates for disease progression or survival in adults or children.[13,16,17] This challenges the usefulness of 6MWD as an end point and has led to a call for alternative, more clinically meaningful end points.

Clinical worsening (CW) has been suggested as an alternative end point in PAH.[18-21] CW consists of a combination of hard unambiguous events such as death and lung transplantation (LTx), and softer events, including hospitalizations, need for additional therapy, and worsening

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of function. CW has been used for some time as a primary or secondary end point in adult trials,[22-39] and its validity has been evaluated in adults.[40] Using 2-year outcome data from the Registry to Evaluate Early and Long-term PAH Disease Management (REVEAL Registry), it was shown that the soft CW end-point components were highly predictive of subsequent mortality.

As 6MWD is not reliable in young children, this end point is not feasible for the pediatric age group. Although not yet evaluated, CW might be an appealing clinical end point in pediatric PAH, since it provides a patient-centered composite end point that decreases the required study participants and it would be applicable in different age groups. Moreover, it would account for the risk of rapid clinical deterioration in children.[8] However, before CW can be used in clinical trials, essential evaluation steps are required that would include a description of how frequent the end-point components of CW occur, how the soft end-point components relate to mortality, and what the timing of CW is compared with mortality.[10] Therefore, the primary aim of this study was to evaluate the usefulness of CW in pediatric PAH by assessing event incidence and prognostic value of each separate component end point and of the composite CW end point. The secondary aim was to describe the timing of CW compared with death or LTx in pediatric PAH.

Materials and Methods

Study Design and Population

This study is a retrospective analysis of data from a prospective clinical registry. In The Netherlands, all children with PAH are referred to the University Medical Center Groningen, which serves as the national referral center of the Dutch National Network for Pediatric Pulmonary Hypertension.[41] Children are followed and registered prospectively according to a standardized protocol. Ethical approval for this ongoing registry was obtained from the institutional review board (medical ethics review board of the University Medical Center Groningen, approval number M11.097816) and the subjects and/or their guardians provided written informed consent at enrollment. All treatment-naive patients in whom PAH-targeted therapy was initiated between January 1, 2000, and January 1, 2014, were included in this study.

End-Point Definition and Data Collection

The definition of CW included the following end-point components: (1) death; (2) LTx; (3) nonelective PAH-related hospitalizations, including hospitalizations for atrial septostomies; (4) initiation of IV prostanoids; and (5) functional deterioration, defined as either worsening of World Health Organization functional class (WHO-FC), $\geq 15\%$ decrease in 6MWD, or both. This CW definition is in-line with various CW end points used in adult PAH trials and as proposed in consensus statements.[42,43] As the change in 6MWD as an end point has been challenged, a sensitivity analysis was performed with defining functional deterioration as worsening of WHO-FC only. The CW components

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