The REVEAL: a registry to evaluate early and long-term Pulmonary Arterial Hypertension disease management

The REVEAL (Registry to Evaluate Early and Long-term PAH disease management) was one of the largest and most ambitious research efforts ever undertaken to study patients with Pulmonary Arterial Hypertension (PAH). As REVEAL grew and long-term data became available, the REVEAL Registry provided the most current picture of the clinical course of PAH, as well as updated data on outcomes of different treatments for patients diagnosed with different types of PAH. Historically, the incidence of PAH has been difficult to measure. Estimates suggest that more than 100,000 people in the United States suffer from PAH. As PAH research grows, we may find that PAH will be diagnosed more often as diagnostic and treatment options improve. In 1981, the National Heart, Lung, and Blood Institute (NHLBI) initiated the National Primary Pulmonary Hypertension Patient Registry in order to better understand the disease. The registry enrolled 187 patients from 32 medical centers in the United States through 1985. Patients were followed prospectively for approximately 5 years. Analysis of the data revealed the following characteristics about patients in the study (1, 2): a 1.7:1 female to male ratio, the mean age at diagnosis was 36.4 years, females tended to present with more severe symptoms, the mean time from onset of symptoms to diagnosis was 2.03 years, right ventricular hypertrophy was found in 87% of patients, right atrial pressure was elevated in 72% of patients, the estimated median survival was 2.8 years, single-year survival rates of 1 year, 68%; 3 years, 48%; and 5 years, 34%.

Subsequent to the NHLBI Registry, data has been published from two European PAH registries. The Pulmonary Hypertension Registry in France (3) collected data from 674 adult patients with PAH from 17 university hospitals between 2002 and 2003. The Swiss Registry (4) retrospectively collected data from 106 patients with severe primary pulmonary hypertension at four university centers.

Registries like REVEAL are studies intended to collect information on a broad population of patients about the natural history of disease and current treatment patterns in the real world.

This registry was different from a randomized clinical trial as no specific treatments was required to be enrolled in REVEAL and few controls were placed on the clinical management of patients. REVEAL was not designed to test any one particular hypothesis about PAH treatment, rather it was intended to generate many hypotheses about which treatments work best for certain types of patients with PAH.

Because of this real-world, observational study design, information from the Registry was intended to complement the data collected in a wide variety of ongoing and future clinical trials. Ultimately, data from REVEAL may help clinicians to design better, more informed clinical trials and treatments for PAH.

The REVEAL Registry is designed to build upon the information collected from previous PAH registries, and it will complement the data collected from a wide variety of current and future randomized clinical trials. In addition to the observational studies mentioned below, there are other PAH registries that seek to measure certain aspects of PAH and population subgroups within the broadly defined classification of patients diagnosed with WHO Group I PAH.

The REVEAL Registry was a multicenter, observational, U.S.-based study of the clinical course and disease management of patients with pulmonary arterial hypertension (PAH). All consecutive consenting newly diagnosed or previously diagnosed patients with World Health Organization (WHO) Group I PAH, who met specific hemodynamic criteria based upon prior performance of right heart catheterization (RHC), at participating institutions were enrolled. Patients were designated as "newly diagnosed" if their qualifying RHC was performed within the 3 months preceding enrolment and "previously diagnosed" if their RHC was prior to the 3 months before enrolment (5). Patients were eligible to be enrolled regardless of the specific treatments received before enrolment or during the study. At the time of study entry, data on past medical history was collected using patient interview and review of the patient's medical record. Thereafter, patients participating in the registry were followed through the end of 2012. 3.515 patients from 55 participating centers across the United States were enrolled and tracked in the REVEAL Registry. Patient enrolment began in March 2006 and continued through December 2009. To ensure generalizability of the results, a variety of academic and community PAH centers were selected to participate in REVEAL. The Registry has been carefully designed to be a broad-based, observational study of patients in the United States with WHO Group I PAH. The study is intended to generate new hypotheses and understandings of the clinical course of patients with PAH and which treatments produce the best outcomes for patients with different underlying forms of the disease.

The objectives of the REVEAL Registry were: to characterize the demographics and clinical course of the patient population diagnosed with WHO Group 1 PAH; to evaluate differences in patient outcomes according to WHO Group I classification subgroup; to compare patient outcomes in patients who do and do not meet prespecified hemodynamic criteria for the diagnosis of PAH; to identify clinical predictors of short-term and long-term outcomes, to assess the relationship between PAH medications, individually and in combination, and patient outcomes; to report temporal trends in treatments and outcomes for newly diagnosed patients; to collect timely and relevant data that will assist in the evolving research needs of the PAH community.

A large number of predictors of outcome have been

identified in patients with PAH. However it is clear from experience that individual predictors do not always (or even usually) align in an individual patient in a consistent direction. A patient may have a pessimistically predictive BNP level, but an optimistic 6MWD. In view of this, it seems appropriate to consider the total information available about a patient in order to arrive at a reasonable conclusion about their severity of disease and outlook for future stability or deterioration.

Therefore the prognostic value of multiple factors to enable more accurate risk stratification was assessed and an algorithm for predicting survival in patients with PAH was developed.

Predictors of survival of 2,716 adult patients meeting traditional haemodynamic criteria were analysed, and risk stratification was proposed based on a prognostic equation. The equation was developed from a multivariable Cox model which identified 15 factors that were associated with increased risk and four factors that were associated with decreased risk. Adjusted for other variables, CTD-APAH, PoPH-APAH and FPAH were identified as being associated with increased risk compared with other WHO group I PAH subgroups. Other factors associated with increased risk were renal insufficiency, males aged 60 yrs, patients with a heart rate of 92 beats/ min or systolic blood pressure <110 mmHg, and patients with pericardial effusion per echocardiography. In the multivariable model, RHC data proved to be predictive only at the extreme ends of the distributions, with higher risk associated with Right Atrial Pressure > 20 mmHg for RHCs performed in the year prior to enrolment and PVR > 32 Wood units. Relative to WHO functional class, patients who were in WHO functional class III were at higher risk and, to an even greater extent were those in WHO functional class IV. Patients who were in WHO functional class I were at lower risk than the higher functional classes. BNP, DLCO % predicted and 6MWD each had higher risk and lower risk cut-off points identified. Thus, while high BNP, low 6MWD and low DLCO are associated with poor outcomes, low BNP, high 6MWD and high DLCO are associated with better than average outcomes. Furthermore the 500 newly diagnosed patients enrolled after September 2007 provided a unique opportunity to validate the prognostic equation utilising data that had not been part of the model development process. Validating a model developed in a primarily prevalent cohort in a different cohort of newly diagnosed patients allows for a robust assessment of the generalisability of the model. Additionally, a simplified version of the equation, the REVEAL risk calculator, was developed prior to validation, and the new patient cohort provided an opportunity to validate both the equation and the calculator. The validation demonstrated excellent discrimination and calibration for both the prognostic equation and the risk calculator. Although a remarkable depth and breadth of data remain to be analysed (and continue to be collected), REVEAL has already provided extensive information about PAH based on broad institutional, geographical, clinical, haemodynamic and demographic diversity. It has characterised features of disease and real-world management at presentation and various stages of progression in subsets of WHO group 1, sex, age, region and severity. Functional and early survival outcomes in the general PAH population and PAH subsets have been described, and predictors of outcome based on a composite of haemodynamic, clinical and functional variables have been identified. Potential practical applications of predictive capabilities in the field of transplantation have been advanced REVEAL provides a perspective about the presentation, management and outcome of PAH in the USA. The future comparison and collaboration with other large registries provide a unique opportunity to further understand differences and similarities in distinct PAH populations.

References

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