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Original article

Trends in Pulmonary Hypertension Over a Period of 30 Years: Experience From a Single Referral Centre

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ABSTRACT

Introduction and objectives: Pulmonary arterial hypertension (PAH) is characterized by increased pulmonary vascular resistance, right ventricular dysfunction and death. Despite scientific advances, is still associated with high morbidity and mortality. The aim is to describe the clinical approach and determine the prognostic factors of patients with PAH treated in a national reference center over 30 years.

Methods: Three hundred and seventy nine consecutive patients with PAH (January 1984 to December 2014) were studied. Were divided into 3 periods of time: before 2004, 2004-2009 and 2010-2014. Prognostic factors (multivariate analysis) were analyzed for clinical deterioration.

Results: Median age was 44 years (68.6% women), functional class III-IV: 72%. An increase was observed in more complex etiologies in the last period of time: Pulmonary venoocclusive disease and portopulmonary hypertension. Upfront combination therapy significantly increased (5% before 2004 vs 27% after 2010; $P < .05$). Multivariate analysis showed prognostic significance in age, sex, etiology and combined clinical variables as they are independent predictors of clinical deterioration ($P < .05$). Survival free from death or transplantation for the 1st, 3rd and 5th year was 92.2%, 80.6% and 68.5% respectively. The median survival was 9 years (95% confidence interval,, 7.532-11.959)

Conclusions: The PAH is a heterogeneous and complex disease, the median survival free from death or transplantation in our series is 9 years after diagnosis. The structure of a multidisciplinary unit PAH must adapt quickly to changes that occur over time incorporating new diagnostic and therapeutic techniques.

La evolución de la hipertensión arterial pulmonar a lo largo de 30 años: experiencia de un centro de referencia

Palabras clave:
Supervivencia
Hipertensión pulmonar
Centro de referencia

RESUMEN

Introducción y objetivos: La hipertensión arterial pulmonar (HAP) se caracteriza por aumento de resistencias vasculares pulmonares, disfunción progresiva del ventrículo derecho y muerte. A pesar de los avances, sigue asociada a alta morbimortalidad. El objetivo del estudio es describir el tratamiento de esta enfermedad y determinar factores pronósticos de pacientes con HAP tratados en un centro de referencia nacional a lo largo de 30 años.

Métodos: Se estudió a 379 pacientes consecutivos diagnosticados de HAP (enero de 1984-diciembre de 2014). Se los distribuyó en 3 intervalos de tiempo: previo a 2004, 2004-2009 y 2010-2014, y se analizaron los factores pronósticos de deterioro clínico.

Resultados: La mediana de edad de los pacientes es 44 años (el 68,6% eran mujeres) y estaban en clase funcional III-IV el 72%. Se observó un incremento en etiologías más complejas: enfermedad venoocclusiva

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e hipertensión portopulmonar en el último periodo. La terapia combinada de inicio aumentó (el 5% previo a 2004 frente al 27% posterior a 2010; p < 0,05). El análisis multivariable mostró como factores independientes de deterioro clínico edad, sexo, etiología y variables combinadas (p < 0,05). La supervivencia libre de muerte o trasplante al primero, el tercero y el quinto año fueron del 92,2, el 80,6 y el 68,5% respectivamente. La mediana de supervivencia fue 9 años (intervalo de confianza del 95%, 7,532-11,959).

Conclusiones: La HAP es una enfermedad heterogénea y compleja. La mediana de supervivencia libre de muerte o trasplante en nuestra serie es 9 años. La estructura de una unidad multidisciplinaria de HAP debe adaptarse con rapidez a los cambios que se producen en el tiempo incorporando nuevas técnicas diagnósticas y terapéuticas.

Abbreviations

6MWT: 6-minute walk test
FC: functional class
LT: lung transplantation
PAH: pulmonary arterial hypertension
PVOD: pulmonary venooclusive disease

INTRODUCTION

Pulmonary arterial hypertension (PAH) is defined as a group of diseases characterized by a progressive increase in pulmonary vascular resistance that leads to right ventricular failure and death. Prognosis is determined by the pathophysiological interaction between the rate of progression of obstructive changes in the pulmonary microcirculation and the adaptive response of the right ventricle. The main known prognostic factor in this disease is the extent of right ventricular dysfunction.

Pulmonary arterial hypertension is a rare disease with an estimated prevalence in different registries of between 15 and 26 cases per million population older than 14 years.[1] Thanks to the scientific community's efforts, more than 30 multicenter clinical trials have been designed and conducted,[2] which have allowed the development of 5 drug classes: prostacyclin analogues, phosphodiesterase-5 inhibitors, guanylate cyclase stimulators, prostacyclin receptor agonists, and endothelin receptor antagonists. These drugs, along with diagnostic and prognostic advances, have revolutionized PAH treatment, as reflected in 3 clinical practice guidelines that encompass the accumulated scientific evidence, published in 2004, 2009, and 2015, respectively.[3–5]

Previously, lung transplantation (LT) was the only treatment available, but following the discovery of various specific drugs, LT is now the final treatment option for patients who do not respond to pharmacological therapy.[3] Despite advances, PAH remains a disease with a high associated morbidity and mortality, with a 5-year survival of 65% in Spain.[1]

The aim of our study was to describe the changes in therapeutic strategies and determine the prognostic factors and long-term survival of a cohort of patients with a diagnosis of PAH, in a national referral center, over a period of 30 years.

METHODS

Study Design and Population

This was an ambispective observational cohort study of patients diagnosed with group 1 PAH (idiopathic, familial, or hereditary PAH, forms associated with connective tissue disease, human immunodeficiency virus [HIV], portal hypertension, rapeseed oil, congenital heart disease, pulmonary veno-occlusive disease, and other less common causes [Osler-Weber-Rendu and hemolytic anemia]) from January 1984 to December 2014, who were treated at the Pulmonary Hypertension Multidisciplinary Unit of the *Hospital Univeristario 12 de Octubre*. The *Hospital Universitario 12 de Octubre* Ethics Committee approved the study. Patients seen from the year 2000 onwards were prospectively included in the database; those seen prior to the year 2000 were retrospectively included. Date of diagnosis was defined as the first right heart catheterization performed. We excluded congenital heart diseases with Eisenmenger syndrome and chronic thromboembolic pulmonary hypertension (Figure 1).

Patients were divided according to 3 time intervals, to coincide with the guidelines available for each period (European Society of Cardiology/European Respiratory Society guidelines) as follows:

- Diagnosis prior to 1 January 2004.
- From 1 January 2004 to 31 December 2009 (2004 guidelines).[4]
- From 1 January 2010 to 31 December 2014 (2009 guidelines).[5]

Diagnosis of PAH was based on a diagnostic algorithm and the hemodynamic criteria recommended in the guidelines from each period.

The following variables were analyzed at diagnosis: demographic data, PAH etiology, functional class (FC), 6-minute walk test (6MWT), right atrial pressure, cardiac output, mean pulmonary artery pressure, pulmonary vascular resistance, pericardial effusion, and initial treatment. The event "clinical deterioration" was defined by the first event to occur: death, inclusion on the LT waiting list, or atrial septostomy.

Statistical Analysis

Descriptive results are presented as frequency and percentage for qualitative variables and mean ± standard deviation or median [interquartile range] for quantitative variables. To calculate the statistical significance ($P < .05$) of comparisons for qualitative variables between groups, the Fisher exact test was used. For quantitative variables with normal distribution, we used the Student *t* test, and analysis of variance for independent groups when 2 or more groups were being compared. Nonparametric tests were used when the variable did not follow a normal distribution.

To identify the parameters that were "predictors of clinical deterioration", bivariate analysis was performed for each variable regarding the time until deterioration; Kaplan-Meier curves and the log-rank test were used to compare the curves. Subsequently, those variables that were statistically significant ($P < .05$) in the bivariate analyses were selected and included in the multivariate Cox regression model for time until deterioration.

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