International Journal of Cardiology 203 (2016) 938–944

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Management and outcomes in chronic thromboembolic pulmonary hypertension: From expert centers to a nationwide perspective

P. Escribano-Subías [a,*,1], R. del Pozo [b,1], A. Román-Broto [c,d], J.A. Domingo Morera [e], A. Lara-Padrón [f], T. Elías Hernández [g], L. Molina-Ferragut [h,i], I. Blanco [d,j], J. Cortina [k], J.A. Barberà [d,j], on behalf of REHAP investigators [2]:

[a] Pulmonary Hypertension Unit, RIC group, Cardiology Department, Hospital Universitario 12 de Octubre, Madrid, Spain
[b] Pulmonary Hypertension Unit, Pneumonology Department, Hospital Universitario 12 de Octubre, Madrid, Spain
[c] Department of Pneumonology, Hospital Universitari Vall d´Hebrón, Universitat Autonoma, Barcelona, Spain
[d] Biomedical Research Networking Center on Respiratory Diseases (CIBERES), Spain
[e] Department of Pneumonology, Hospital Universitario Miguel Servet, Zaragoza, Spain
[f] Department of Cardiology, Hospital Universitario de Canarias, Santa Cruz de Tenerife, Spain
[g] Department of Pneumonology, Hospital Universitario Virgen del Rocío, Sevilla, Spain
[h] Department of Cardiology, Hospital del Mar, Barcelona, Spain
[i] Heart Diseases Biomedical Research Group, IMIM (Hospital del Mar Medical Research Institute), Barcelona, Spain
[j] Department of Pulmonary Medicine, Hospital Clínic-IDIBAPS, University of Barcelona, Barcelona, Spain
[k] Pulmonary Hypertension Unit, Cardiac Surgery Department, Hospital Universitario 12 de Octubre, Madrid, Spain

ARTICLE INFO

Article history:
Received 6 August 2015
Received in revised form 19 October 2015
Accepted 4 November 2015
Available online 10 November 2015

ABSTRACT

Background: The Spanish "Registry of Pulmonary Arterial Hypertension" (REHAP), started in 2007, includes chronic thromboembolic hypertension (CTEPH) patients. Based on data provided by this registry and retrospective data from patients diagnosed during 2006 (≤12 months since the registry was created), clinical management and long-term outcomes of CTEPH patients are analyzed nationwide for the first time in a scenario of a decentralized organization model of CTEPH management.

Methods and results: A total of 391 patients (median [Q1:Q3] age 63.7 [48.0;73.3] years, 58% females) with CTEPH included during the period January 1, 2006–December 31, 2013 in the REHAP registry were analyzed. Rate of pulmonary endarterectomy (PEA) was 31.2%, and highly asymmetric among centers: rate was 47.9% at two centers designated as CTEPH expert centers, while it was 4.6% in other centers. Among patients not undergoing PEA, 82% were treated with therapies licensed for pulmonary arterial hypertension (PAH). Five-year survival rate was 86.3% for PEA patients, and 64.9% for non-PEA patients. Among non-PEA patients, presenting proximal lesions (42% of non-referred patients) was associated with a 3-fold increase in mortality. PEA patients achieved significantly better hemodynamic and clinical outcomes at one-year follow-up compared to non-PEA patients. Patients not being referred for PEA assessment were older and had a worse functional capacity. Older age was the most deterrent factor for non-operability.

Conclusion: Despite the increase in diagnosis and expertise in PEA-specialized centers, an important percentage of patients do not benefit of PEA in a decentralized organization model of CTEPH management.

1. Introduction

Chronic pulmonary thromboembolic hypertension (CTEPH) is one of the leading causes of severe pulmonary hypertension (PH) and as such, it is associated with significant morbidity and mortality [1,2]. Even though recognition of CTEPH has recently increased [3], epidemiological data are scarce [3,4] and there is an urgent need to identify patients.

Pulmonary endarterectomy (PEA) is the treatment of choice for CTEPH patients given its potential to cure the disease [5], with restoration of hemodynamics to normal or nearly normal and improvement in clinical symptoms in most patients [3,6,7]. PEA is performed in highly specialized centers, and outcomes are associated with growing expertise in the technique, optimal patient selection, and better perioperative management [3,8]. Until the launch in 2015 of riociguat – currently the only treatment licensed for CTEPH – which has demonstrated to significantly improve exercise capacity and PVR in CTEPH patients deemed

* Corresponding author at: Pulmonary Hypertension Unit, Cardiology Department, Hospital Universitario 12 de Octubre, Complutense University, Madrid, Crtra. Andalucia km 5,400, 28041 Madrid, Spain
E-mail address: pilar.escribano.subias@gmail.com (P. Escribano-Subías).
[1] These two authors contributed equally to this work.
[2] REHAP: Registro Español de Hipertensión Arterial Pulmonar (Spanish Registry of Pulmonary Arterial Hypertension). A full list of REHAP investigators is given in the Appendix.

http://dx.doi.org/10.1016/j.ijcard.2015.11.039
0167-5273/

inoperable or those with residual PH after PEA [9,10], patients were treated with medical therapies proven to be effective in pulmonary arterial hypertension (PAH) [5].

Current knowledge on the outcomes associated with the management of CTEPH arises precisely from these PEA-specialized centers [3,11]. However, this information is far from capturing outcomes of CTEPH patients at a nationwide perspective since country-specific management issues, and specifically how referral for PEA assessment is undertaken (i.e. mandatory and centralized in reference centers vs. optional and based on a decentralized decision-making model), may greatly influence outcomes at this level. These kinds of analyses, which are fundamental to outline policies for CTEPH management, are scarce and only available from countries where a centralized model is followed [3,12].

A national observational registry of pulmonary arterial hypertension (REHAP) has been running in Spain since 2007 providing valuable information about CTEPH epidemiology and survival [4]. This registry is one of the largest currently in place in Europe. One of its objectives was to evaluate the clinical management of CTEPH patients and long-term outcomes under a nationwide perspective, according to the management organization model established. This model is characterized for being decentralized, with management of patients (i.e. diagnosis and treatment, some of them including PEA) taking place at so-designated PH-specialized centers and at general hospitals. In centers not performing PEA, decision regarding referral for PEA assessment is left to doctor's judgment. Two of the PH-specialized centers bring together most CTEPH patients and are designated as expert centers.

The REHAP offers therefore a unique opportunity to analyze from a nationwide perspective how patients are treated and long-term outcomes according to treatment in a decentralized model of CTEPH management. This is also especially interesting since only a few long-term evidence of outcomes in CTEPH patients receiving PAH-specific therapies is currently available [3]. Other data of interest such as how patient selection for PEA assessment is undertaken when left to doctor's judgment is also provided.

2. Methods

2.1. Study subjects

Analyzed CTEPH patients were included in the REHAP registry from January 1, 2006 to December 31, 2013. Patients diagnosed during 2006 (≤12 months since the registry was created) were included retrospectively, and prospectively thereafter. Centers reporting data to the registry included 31 PH-specialized centers and general hospitals, which covered 15 of the 17 administrative regions of Spain. Two of these centers managing more than 50 CTEPH patients (those belonging to the health administrative area and those being referred for PEA assessment) are considered CTEPH expert centers. As such, they participate at the International CTEPH registry [11].

Study design, inclusion criteria and data collection have been previously described [4,13]. Summarizing, registered patients were older than 14 years and met the modified definition of CTEPH [14] and prespecified hemodynamic criteria by right heart catheterization (RHC) before study entry (mean pulmonary artery pressure [mPAP] ≥ 25 mmHg, pulmonary capillary wedge pressure or left ventricular end-diastolic pressure ≤ 15 mmHg or 16–18 mmHg if justified [11] and PVR ≥ 3 Wood units). All patients showed perfusion defects by ventilation/perfusion lung scintigraphy and CT angiography consistent with CTEPH. Patients showing a FEV_1 < 60% were included if they met all other inclusion criteria. All patients received anticoagulation therapy for at least three months before a CTEPH diagnosis, and continued receiving it chronically.

2.2. Follow-up

Data were obtained from assessments routinely performed in clinical practice, and included demographic (age and gender) and anthropometric parameters, PH clinical characteristics, and diagnostic parameters (echocardiography and RHC). Lesion proximity was assessed by computed tomographic angiography. Lesions affecting main and lobar arteries were considered proximal lesions. Decision to operate was based on the judgment of the multidisciplinary team of each centre and was based on lesion accessibility, hemodynamic status and presence of co-morbidities. Haemodynamic residual PH was defined as having a mPAP ≥ 25 mmHg at rest [5]. Clinically relevant PH was defined as also having a PVR ≥ 5 Wood units [15]. Both, all-cause and PH-related causes of death (heart failure and sudden death) were collected. The protocol was reviewed and approved by the Institutional Review Board of the Hospital de Cruces, Bilbao, Spain.

2.3. Statistical analysis

Continuous variables were expressed as mean (standard deviation [SD]) or as median with first and third quartiles (Q1;Q3) when not normally distributed. Comparisons were made using the paired *t* test for parametric data or the U-Mann Whitney test for non-parametric data. Categorical variables were expressed as n (%) and compared using the Chi-square test or Fisher's exact test, as appropriate. All P-values were two-sided, with a P-value <0.05 being considered statistically significant.

Univariate Cox's proportional-hazard regression models were used to assess the relationship between patient characteristics and both, the likelihood to undergo PEA and mortality. The selection of patients' characteristics potentially associated with mortality or with the likelihood of undergoing PEA was made on the basis of published data [3,6,11,16] and own expertise. Only variables available in >70% patients were chosen. Co-linearity between variables was examined. Variables identified in this analysis (P-value <0.2) were included in a forward stepwise multivariate Cox's proportional hazards model in order to identify independent risk factors. A 95% confidence interval (CI) was considered in PEA and mortality models.

Survival was estimated using the Kaplan–Meier analysis. The study date of entry was defined as the date of the first diagnostic RHC. Patients were followed-up until the censoring date of December 31, 2014 or the date of death. For survival analysis, patients lost to follow-up were censored at the time of their last visit or observation. All-cause mortality was defined as the end-point and the log-rank test was used for comparison between groups. Outcomes at one year were also analyzed (follow-up analysis). For this purpose, the visit date closer to one year was chosen. Patients included in the follow-up analysis were those with a follow-up visit 4 months after PEA or at initiation of medical treatment when no PEA was performed. Overall change (Delta value) was calculated for the most prominent variables indicating prognosis. All statistics were performed using SPSS version 17 (SPSS Inc., Chicago, IL, USA).

3. Results

3.1. Study population

A total of 391 CTEPH patients meeting the inclusion criteria had been included in the registry by December 2013, and constituted the study population. Patients presented a median age (Q1;Q3) of 63.7 (48.0;73.3), were women in 58% of cases and had a severe clinical and hemodynamic condition (Table 1).

3.2. Treatment at diagnosis

Among all patients, 122 (31.2%) underwent PEA during this period (hereafter PEA patients). Of these, 115 PEAs (94% of all PEAs) took