CLINICAL RESEARCH

Mexican registry of pulmonary hypertension REMEHIP☆

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Abstract
Objective: REMEHIP is a prospective, multicentre registry on pulmonary hypertension. The main objective will be to identify the clinical profile, medical care, therapeutic trends and outcomes in adult and pediatric Mexican patients with well-characterized pulmonary hypertension.
Methods: REMEHIP a multicenter registry began in 2015 with a planned recruitment time of 12 months and a 4-year follow-up. The study population will comprise a longitudinal cohort

study, collecting data on patients with prevalent and incident pulmonary hypertension. Will be included patients of age >2 years and diagnosis of pulmonary hypertension by right heart catheterization within Group 1 and Group 4 of the World Health Organization classification. The structure, data collection and data analysis will be based on quality current recommendations for registries. The protocol has been approved by institutional ethics committees in all participant centers. All patients will sign an informed consent form.

Currently in Mexico, there is a need of observational registries that include patients with treatment in the everyday clinical practice so the data could be validated and additional information could be obtained versus the one from the clinical trials. In this way, REMEHIP emerges as a link among randomized clinical trials developed by experts and previous Mexican experience.

Registro Mexicano de Hipertensión Pulmonar REMEHIP

Resumen

Objetivo: REMEHIP es un registro prospectivo, multicéntrico en hipertensión pulmonar. El objetivo principal será identificar el perfil clínico, atención médica, tendencias terapéuticas y evolución en pacientes mexicanos adultos y pediátricos con hipertensión pulmonar bien caracterizada.

Métodos: El REMEHIP comenzó en el año de 2015 y se planea un reclutamiento de 12 meses con un seguimiento de 4 años. La población en estudio será una cohorte longitudinal y se obtendrán datos de pacientes prevalentes e incidentes con hipertensión pulmonar. Se incluirán pacientes con edad > 2 años con diagnóstico de hipertensión pulmonar demostrado por cateterismo cardiaco derecho del Grupo 1 y Grupo 4 de la clasificación de la Organización Mundial de la Salud. La estructura, colección de datos y el análisis se establecerá a través de las recomendaciones actuales de calidad para los registros. El protocolo ha sido aprobado por los comités de ética de todos los centros participantes. Todos los pacientes firmarán un consentimiento informado.

Actualmente en México existe una necesidad de registros observacionales que incluyan a pacientes con tratamiento en la práctica clínica cotidiana, de tal forma que los datos obtenidos podrían validarse y el resto de la información podría compararse con la derivada de los estudios clínicos. De esta forma REMEHIP surge como un vínculo entre los estudios clínicos aleatorizados conducidos por expertos y la experiencia mexicana previa.

Introduction

Pulmonary hypertension (PH) is a worldwide distribution group of vascular diseases characterized by a progressive increase in pulmonary vascular resistance and pulmonary arterial pressure, with secondary vascular and right ventricular (RV) remodeling, RV dysfunction, heart failure syndromes,[1] and finally, premature death.[2] In developed countries, major medical advances had occurred in the past two decades, including more systematic assessment and availability of new therapeutic approaches. In addition, current registries have reported new data on epidemiology, demography, clinical presentation, treatment, and prognosis.[3–7] However, evidence from developing countries is scarce,[5] and more information is necessary to identify current care strategies such populations. High-quality clinical registries[8,9] may help us to understand if the knowledge

acquired from clinical trials is being properly applied, and whether their results are reproducible in day-to-day clinical practice. The results of the Registro Mexicano de Hipertensión Pulmonar (REMEHIP), a registry with a 4-year follow-up, will hopefully broaden our knowledge regarding clinical profile, medical care, therapeutic trends, and outcomes in adult and pediatric Mexican patients with well-characterized PH.

REMEHIP design

REMEHIP is a multicenter, longitudinal cohort study, collecting data on patients with prevalent and incident PH. The primary objective is to identify clinical characteristics, treatment trends, and in-hospital and 4-year outcomes, in terms of major adverse cardiovascular events (MACE).

Inclusion criteria are patients of age >2 years and diagnosis of PH,[10] within a Group 1 and Group 4 of the World Health Organization (WHO) PH classification.[10] Exclusion criteria are severe pulmonary function abnormalities (vital capacity <60% predicted, forced expiratory volume in 1 s <50% predicted); abnormal pulmonary capillary wedge pressure; and refusal to participate. The registry is has been approved by local ethics committees of the participating centers.

Variables to be included

The following variables are to be included for all patients: date of symptom onset; medical history; personal and family history; treatment at enrollment; physical examination; WHO functional class; 6-minute walk distance; electrocardiogram (ECG); chest x-ray; echocardiogram; pulmonary function tests; v/Q lung scan and/or pulmonary angiography and/or pulmonary angiotomography; right heart catheterization and, whenever possible, acute vasodilator challenge[11,12]; biomarkers (troponin I, B-type natriuretic peptide [BNP], D-dimer); international normalized ratio (INR) for patients on a vitamin K antagonist; current treatment; in-hospital and follow-up outcomes; and MACE.

Office visits

Data will be collected at the time of the first outcome and updated at each follow-up visit, and will comprise expected PH symptoms; WHO functional class; current treatment and dose; patient adherence to treatment; side effects; concomitant medication; body weight; blood pressure; heart and respiratory rates; biomarkers, when they play a role in the standard of care, whenever possible or feasible; and INR in patients receiving oral anticoagulation with a vitamin K antagonist.

Sites

Both experienced and inexperienced sites will participate in this registry. The former will involve sites (outcome treatment and tertiary centers) in which investigators are experienced in the diagnosis, stratification, and treatment of patients with PH. Centers without expertise, but with facilities for diagnosis and stratification (6-minute walk distance, pulmonary function tests, v/Q lung scan and/or pulmonary angiography, right heart catheterization and biomarkers), will be included provided they adhere to the protocol.

Quality criteria

The following criteria will be used to improve the quality of the data: standardized definitions, data and report reviews; tools for fast feedback; meetings among principal investigators and the steering committee (at least one meeting per year); ethics procedures review; electronic, simple and accessible data collection; rigorous center selection, based on investigators expertise and/or facilities and resources; consecutive patient enrollment to obtain a representative sample; random audit of centers; centralized data storage and statistical analysis; reporting of all data and consistent conclusions; and transparency of funds for any publication.[8,9] The quality of this registry will also be measured by the number of publications and presentations at national and international meetings, as has been done previously.[12]

Data collection

The electronic database will have 178 variables, including, among others, data on symptoms at onset; medical history; personal and family history; physical examination; 6-minute walk distance; treatment; ECG; chest x-ray; echocardiogram; pulmonary function tests; v/Q lung scan; pulmonary angiography; right heart catheterization; acute vasodilator challenge; biomarkers; and (at follow-up) MACE.

Study definitions

PH is defined as mean pulmonary arterial pressure ≥25 mmHg at rest. Pulmonary arterial hypertension (PAH) (group 1 of the current clinical classification),[10] is defined as mean pulmonary artery pressure ≥25 mmHg with pulmonary artery wedge pressure ≤15 mmHg or left ventricular diastolic pressure ≤15 mmHg at right heart catheterization, with normal or reduced cardiac output or pulmonary vascular resistance >3 Wood units.

Chronic thromboembolic pulmonary hypertension: patient with PH (confirmed by right heart catheterization) with lung lobar or segmental perfusion defects (v/Q scan, CT angiography, pulmonary angiography) with no prior history of acute pulmonary embolism. Patient with PH after acute pulmonary embolism with at least 3 months of effective anticoagulation therapy.

Diastolic pulmonary pressure gradient is defined as diastolic pulmonary arterial pressure minus mean pulmonary capillary wedge pressure.

Abnormal pulmonary capillary wedge pressure is defined as capillary wedge pressure >15 mmHg.

Positive vasodilator response is defined as a reduction in mean pulmonary arterial pressure of ≥10 mmHg, leading to a value ≤40 mmHg, with a normal or high cardiac output.

A severe pulmonary function abnormality is defined as a pulmonary function test with forced vital capacity, total lung capacity or FEV1 <60% of predicted.

An early state of RV dysfunction is defined as tachycardia with RV third heart sound and/or loss of accentuation of pulmonary component of the second heart sound, without peripheral signs of systemic venous hypertension.

An established state of RV dysfunction is defined as tachycardia, with or without RV third heart sound, with or without loss of accentuation of pulmonary component of the second heart sound, and peripheral signs of systemic venous hypertension.

Clinical findings to in-patient treatment are defined as tachycardia and severe respiratory failure in addition to severe signs of systemic venous hypertension and low cardiac output, auricular or ventricular arrhythmias, pulse oximetry <90% or BNP >400 pg/dL.

Tachycardia is defined as heart rate >90 beats/min. Tachypnea is defined as respiratory rate >30 breaths/min.

Hypotension is defined as diastolic blood pressure $\leq$60 mmHg and or systolic blood pressure <100 mmHg.

Systemic venous hypertension is defined as jugular distention, liver enlargement, and leg edema. Severe systemic venous hypertension is defined as peripheral signs of systemic venous hypertension plus pleural or pericardial effusion and ascites.

MACE is defined as in-hospital or outpatient heart failure, cardiogenic shock, syncope, cardiovascular death, or bleeding complications.

Cardiogenic shock in the setting of severe RV dysfunction is defined as systolic blood pressure <90 mmHg despite the use of vasoactive amines, signs of low cardiac or renal output, adrenergic hyperactivity, metabolic acidosis, and BNP >600 pg/dL.

Cardiovascular death is defined as secondary to right heart failure, cardiogenic shock, or auricular or ventricular arrhythmia.

Standard treatment is defined as the use of digoxin, furosemide, spironolactone, nifedipine, or other calcium channel blockers, oral anticoagulants, or oxygen therapy.

Specific treatment is defined as the use of endothelin receptor antagonists, prostanoids, phosphodiesterase-5 inhibitors, stimulators of soluble guanylate cyclase or prostacyclin-receptor agonists.

Prevalent: patient with PH (confirmed by right heart catheterization) and more than 3 months of diagnosis who is alive.

Incident: patient with PH (confirmed by right heart catheterization) with diagnosis within the 3 months prior to enrollment.

Follow-up

This protocol requires a 4-year follow-up, involving at least two patient visits per year.

Study registration

The study has been registered at ClinicalTrials.gov: NCT02252705.

Statistical analysis

Differences between continuous variables with a normal distribution will be examined using Student's t test. The Wilcoxon rank sum test will be used when continuous variables have failed in normality tests. To analyze categorical variables, χ^2 will be used with Fisher's exact test or Yates's correction. A two-tailed test with a P value <0.05 will be considered as statistically significant. Logistic regression analysis will be used to select independent predictors from those variables that obtain a P value <0.01 by univariate regression analysis. To avoid confusion, the relationship between historical variables for atherosclerosis and cardiovascular events will be examined through logistic regression and multivariable analysis. A Cox proportional risk multivariable model will assess the relationship between each of these variables. Kaplan–Meier survival curves and a Cox proportional risk model will be used for adjusted survival analysis. A P value <0.05 will be considered as statistically significant. Data will be expressed as percentages, means and standard deviations, and odds ratios with 95% confidence intervals.

Considerations

The main goal of evidence-based medicine is to guide therapeutic decisions. The best evidence comes from studies where both or all treatment groups are representative of the patient population. A crucial problem with many randomized controlled trials is that the treatment groups are similar to one another, but not to the population treated in clinical practice.[9] In addition, higher-risk patients are not adequately represented in randomized trials; they are older and are more likely to have comorbid conditions. Registries therefore have an important role in validating trial findings in groups that were excluded or under-represented in randomized trials. Prospective registries that include quality criteria provide important additional information in terms of real-life clinical practice.[8,9]

To our knowledge, the REMEHIP is the first prospective national registry to include incident and prevalent cases of PH in Mexico. Data from the southern hemisphere are scarce, making it difficult to compare these data directly with data from Europe,[4] Asia[5] and the USA.[3] Recently, data from a Brazilian prospective registry, which included 178 patients with newly diagnosed pulmonary arterial hypertension (PAH), showed differences in terms of sex, functional class III or IV ratio, and PAH associated with schistosomiasis infection. In addition, the majority of patients were receiving monotherapy with phosphodiesterase-5 inhibitors, while a low proportion received endothelin receptor antagonists or a combination therapy.[13] The distribution of PAH etiologies and the baseline characteristics of this registry clearly differ from the previously published registries from Europe and the USA.[3,4] These differences highlight the importance of regional registries, and also raise questions about the need to better account for such differences in future clinical trials.

Current and past evidence regarding PH in Mexico comes from data in clinical trials[14,15] and single center registries[16,17] in single centers. In a well-characterized population with right heart catheterization, PAH patients were younger, had low incidence of functional class III or IV, and low mortality,[14,15,17] when compared with patients in registries from developed countries.[3,4] No differences were observed between PAH patients in clinical trials[14,15] and the RENEHAP registry.[17] Recently, 71 newly diagnosed patients with chronic thromboembolic PH were included in the REPHPISSSTE registry.[16] The results of this study are limited due to the fact that right heart catheterization was not routinely performed and diagnosis was driven by CT angio-tomography and echocardiography findings, and the percentage of patients lost to follow-up was high (30%). Also, phosphodiesterase-5 inhibitors and non-vitamin K antagonist oral anticoagulants were used ''off-label'' in most patients, and although chronic thromboembolic PH is a potentially curable form of PH, only one patient underwent pulmonary endarterectomy.

Currently, therefore, there is a need in our country for a national observational registry of adults and pediatric

patients with PH proved by right heart catheterization and treated in everyday clinical practice, to test the external validity of trial data and to provide information that complements data from clinical trials.[18] REMEHIP emerges as a link between randomized controlled trials, registries in developed countries, and previous Mexican experience.[14–17]

Ethical disclosures

Protection of human and animal subjects. The authors state that for this investigation no experiments have been performed on humans or animals.

Confidentiality of data. The authors state that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors state that in this article there are no patient data.

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Conflict of interest

The authors declare no conflict of interest.

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