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β3 ADRENERGIC AGONIST TREATMENT IN CHRONIC PULMONARY HYPERTENSION SECONDARY TO HEART FAILURE: RANDOMIZED, PLACEBO-CONTROLLED PHASE 2 CLINICAL TRIAL

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1. Project summary

Pulmonary hypertension, which implies an elevation of blood pressure in the pulmonary arterial circuit, is a common complication in patients with heart disease, resulting in an aggravation of symptoms and a worsening of the prognosis. This pulmonary hypertension is especially serious when it is associated with a component of vasoconstriction and arterial remodeling, characteristic of combined pre- and post-capillary pulmonary hypertension, since it causes a greater failure of the right ventricle (which has to pump the blood into a circuit with high pressures) which results in hepatic, renal and progressive edema.

Currently we do not have any pharmacological treatment to treat pulmonary hypertension secondary to heart disease. The sympathetic nervous system is essential in the neurohumoral regulation of cardiovascular function and is involved in various cardiopulmonary diseases, including pulmonary hypertension. In recent years, several publications have demonstrated the cardioprotective effect of β3 adrenergic receptor stimulation in different experimental models of ischemia-reperfusion damage and heart failure. Specifically in pulmonary hypertension, preclinical research conducted by researchers of the current project showed that treatment with β3 adrenergic receptor agonists produced a beneficial effect on pulmonary hemodynamics, right ventricular function and pulmonary arterial remodeling.

A β3 adrenergic receptor agonist called mirabegron is currently available and has demonstrated a good safety profile in healthy subjects and patients with overactive bladder syndrome (used to relax bladder smooth muscle).

Thus, the hypothesis of the present project was that treatment with mirabegron in patients with pulmonary hypertension secondary to heart disease will result, in comparison with placebo, in an improvement in pulmonary hemodynamics, right ventricular function, symptoms and exercise tolerance without causing a significant increase in adverse events.

The project was designed with the objective of evaluating the efficacy and safety of this new therapeutic approach (treatment with β3 adrenergic receptor agonists) in patients with combined pre- and post-capillary pulmonary hypertension secondary to

heart disease, by conducting a phase-2 multicenter blind, randomized, placebo-controlled clinical trial.

The main efficacy objective defined was the change in pulmonary vascular resistance at 16 weeks of treatment with respect to the baseline measurement evaluated by right heart catheterization. In addition, secondary objectives were defined regarding clinical parameters, quality of life, safety, hemodynamics and functionality of the right ventricle.

For a correct evaluation candidate patients who wished to participate in the study were evaluated by means of a quality of life questionnaire, blood test, electrocardiogram, echocardiogram, 6-minute test and cardiac magnetic resonance at baseline and after 16 weeks of treatment, at which time the right cardiac catheterization was repeated. During the first 8 weeks the dose of the study medication was progressively titrated. The study was blind, so neither the patient nor the doctor knew if the treatment was mirabegron or placebo.

To reduce the variability of the measures, all imaging tests (echocardiography, magnetic resonance imaging, and computed tomography if resonance was contraindicated) were analyzed blindly in an imaging corelab at the National Center of Cardiovascular Research (CNIC).

The prespecified number of patients necessary to have sufficient statistical power was 62 (31 patients per group). We estimated a 20% loss of follow-up, so the expected number of recruited patients needed was 80.

2. Results

The clinical trial was registered in the databases EUDRA (2016-002949-32) and Clinicaltrials.gov (NCT02775539) under the name SPHERE-HF (β3-adrenergic agoniSt treatment in chronic Pulmonary HypERtEnsion secondary to Heart Failure).
All the necessary steps were taken to guarantee the correct execution of the clinical trial including the approval by the ethical committees of the 4 hospitals participating in the recruitment (Hospital Clínic, reference center; Hospital de la Santa Creu i Sant Pau;

Hospital 12 de Octubre; and Puerta de Hierro Hospital), approval by the Spanish Agency of Medicines and Health Products (AEMPS), authorization for the pharmacy of the Hospital Clínic to mask the study medication and send it to the different recruitment centers, the implementation of pharmacovigilance systems, the development of all NTPs (standard work procedures) and initial visits in the four hospitals for the formation of work teams.

In June 2017 recruitment was opened in Hospital Clinic and by October of that year the 4 centers were open. Since then, a total of 65 patients have been recruited out of the 80 patients that constitute the estimated sample size. However, of these 65 patients, only 7 have been lost of follow-up (10% much lower than the estimated 20%), so actually we have 90% of the necessary sample size. We have not registered any adverse event considered very serious, and in fact the patients who have discontinued the study have done so mostly for reasons outside the tolerance or safety of the treatment. A previously selected Clinical Events External Committee has been blindly evaluating adverse events in the two groups without finding evidence of differences, which demonstrates the safety of mirabegron in this pathology.

As it is a randomized, blind clinical trial that has not yet been closed, we do not have efficacy data. Having achieved 90% of the recruitment of a multi-center trial with very strict eligibility criteria and investigators-driven (without industry intervention) can be considered a success. Recruitment is expected to be completed in the next 4 months.

3. Relevance and future implications

Pulmonary hypertension significantly worsens the quality of life and prognosis of patients with heart failure. It is a very prevalent pathology and there is no pharmacological therapy that has shown a consistent beneficial effect. The current project focuses on the development of a new therapeutic approach for patients with pulmonary hypertension secondary to heart disease, aimed at improving quality of life, functional capacity and, eventually, survival.

Pending the definitive results of efficacy and safety of the trial, if these are positive, SPHERE-HF may modify the treatment standards of these patients since it would

become the first therapy showing a benefit in this pathology. If so, our project will therefore make an important contribution to the quality of life and prognosis of patients with pulmonary hypertension and heart disease in Catalonia and globally, as well as contributing to the reduction of costs of European healthcare systems.

In addition, our project aims to develop new imaging protocols for non-invasive monitoring of patients with pulmonary hypertension using echocardiography and / or cardiac magnetic resonance. The use of new non-invasive algorithms that allow us to avoid repeated cardiac catheterizations would also have a significant impact on the quality of life of patients and the costs of the healthcare system. Thus, we believe that our project will generate new intellectual property, which will stimulate growth and competitiveness in Catalonia and Europe. A part of the intellectual property will have the form of patents of products that cover the new therapeutic approach but there will also be intellectual property opportunities related to the innovations of the developed image protocols. The transfer of innovation from the project to the market will be the next key step to maximize the project impact and highlight the role of the Fundació La Marató TV3 in innovation.

4. Scientific Bibliography Generated

Publications

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