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Protocol

Long-term effect of subcutaneous treprostinil in patients with pulmonary hypertension: rationale and design of the phase IV, multicentre, observational TREPAR-HP study

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ABSTRACT

Background: Pulmonary hypertension (PH) is a chronic, progressive condition with high morbidity and mortality due to right heart (RH) failure. Prognosis depends on RH adaptability and remodelling in response to increased pulmonary arterial pressure. There is little information regarding risk variables and prognostic factors in the Argentinian population, current risk scores have not been validated, and its impact on free-event survival is still unknown. Prostacyclin analogues are the first-line treatment for high-risk patients. However, there is limited evidence on its clinical benefits, long-term effects, and impact on RH remodelling in the Argentinian population.
Methods: The study was designed as a national, multicentre, prospective, observational, phase IV study including 100 patients with pulmonary arterial hypertension or chronic thromboembolic pulmonary hypertension, treated with subcutaneous treprostinil and followed up for 48 months. The study will be conducted in parallel with the patients' standard management and treatment in each centre. The primary objective is to assess the long-term improvement or reversal of RH remodelling (RHRR) parameters obtained by echocardiography. Secondary objectives include the evaluation of the prognostic value of RHRR parameters and the rate of clinical events, the treatment effect in terms of pulmonary vascular resistance, right ventricle systolic function, morbidity and all-cause mortality, quality of life, and safety and tolerability.
Conclusions: This study will help to determine the clinical benefits, long-term effects, and impact on RH remodelling of prostacyclin analogues in Argentina.
Trial registration: The trial was registered at Registro Nacional de Investigaciones en Salud (RENIS) in Argentina (https://sisa.msal.gov.ar/sisa/#sisa; registration number IS003303).

Keywords: Observational study, Pulmonary hypertension, Protocol, Phase IV trial, Treprostinil

INTRODUCTION

Pulmonary hypertension (PH) is a chronic, multifactorial condition characterised by a progressive and sustained increase in the pulmonary vessels resistance (PVR) that impacts the patient's quality of life and may eventually lead to right ventricular (RV) failure and premature death.[1]

According to the underlying pathology, haemodynamic characteristics, and therapeutic approaches, PH is clinically classified into five categories.[1] Rare forms include pulmonary arterial hypertension (PAH; group 1) and chronic thromboembolic pulmonary hypertension (CTEPH) and other pulmonary artery obstructions (group 4). More common forms, with usually mild elevations of pressure, are seen in PH due to left heart disease (group 2), lung disease and/or hypoxia (group 3) or associated with unclear and/or multifactorial mechanisms (group 5).[1] In Latin America, observational studies have shown that the most frequent aetiologies associated with PH are left heart failure (group 2; 55%), chronic obstructive pulmonary disease (group 3; 42%), and PAH (group 1; 3%).[2]

The mean age at diagnosis in current PAH registries is between 50 and 65 years, although it is more frequently diagnosed in the elderly population.[1] With the advent of new therapeutic schemes, survival rates have increased up to 89%-92% at 1 year and 58%-92% at 3 years across studies conducted in Asia, Europe, and the US.[3] In Latin America, data on the epidemiological profile of PAH are scarce, and survival rates vary between regions, with the highest figures reported by Argentinian registries (94% and 83% at 1 and 3 years, respectively).[4-6]

The initial pathophysiological mechanism leading to PAH involves endothelial dysfunction, generating an imbalance between vasoconstrictor, inflammatory, and prothrombotic factors (e.g. endothelin and thromboxane A2) and vasodilator, antiproliferative and anticoagulant factors (e.g. prostaglandin and nitric oxide [NO]).[7] These alterations, among others, generate a favourable scenario for the development of pulmonary vasoconstriction, endothelial cell proliferation, remodelling of the pulmonary vascular bed, and *in situ* thrombosis.[7] The proliferative changes in smooth muscle cells, the pro-inflammatory scenario, and the increased remodelling determine structural changes in the pulmonary vessels, which develop medial hypertrophy and intimal and adventitial thickening, triggering increased vascular tone and pulmonary vascular resistance (PVR).[7]

Diagnosis is usually first suggested by echocardiography, and the confirmation requires right heart catheterisation (RHC). According to the latest recommendations of international guidelines, the haemodynamic diagnosis of PH is established when the mean pulmonary arterial pressure (mPAP) value is >20 mm Hg as assessed by RHC at rest.[8] However, to distinguish whether this elevation is due to pulmonary vascular disease, increased cardiac output, or increased pulmonary arterial wedge pressure (PAWP), the definition of pre-capillary PH has been included in the definition.[8] Thus, increased mPAP with concomitant pulmonary arterial wedge pressure (PAWP)≤15 mm Hg and PVR≥3 Wood units (WU) confirm the presence of pre-capillary PH. Conversely, in groups 2 and 5, a PAWP>15 mm Hg and <3 WU determines the presence of isolated post-capillary PH, and a PAWP>15 mm Hg and ≥3 WU combined pre- and post-capillary PH.[8]

There are no PH-targeted medications approved for PH groups 2 and 3. The therapeutic approach for these patients primarily focuses on treating comorbid conditions (e.g., systemic hypertension or valvular heart disease).[1] Conversely, pharmacological therapies that target the pulmonary vasculature are currently approved for patients with PAH and selected patients with CTEPH.[1] These therapies target the three main signalling pathways regulating pulmonary vasomotor tone and vascular cell proliferation:[1] 1) the NO/cGMP pathway, targeted by phosphodiesterase type 5 (PDE5) inhibitors (such as tadalafil, sildenafil, vardenafil) or soluble guanylate cyclase (sGC) stimulators such as riociguat; 2) the endothelin 1 pathway, targeted by endothelin receptor antagonists (ERAs) such as bosentan, ambrisentan, and macitentan; and 3) the prostacyclin signalling targeted by prostacyclin analogues or prostanoids (e.g., beraprost, epoprostenol, treprostinil, and iloprost), or selective prostacyclin (Ip) receptor agonists (selexipag).

Prostacyclin analogues, widely used in Argentina, are one of the treatments of choice in patients with PAH and the first-line option for those in the high-risk category.[1] Treprostinil exerts a direct vasodilatation of the pulmonary and systemic arterial vascular beds, thus decreasing PAP.[9] Compared to other prostanoids, it has the advantage of being stable at neutral pH and room temperature and can be adminsitered through subcutaneous, intravenous (IV), oral, or inhaled routes of administration.[10] Although clinical studies have shown the efficacy of all modes of delivery, SC infusion is the preferred formulation over the IV route, as it circumvents the need for intravenous lines that could be sources of catheter-related complications such as infection, sepsis, or thrombosis.[1, 10] Evidence of SC treprostinil clinical efficacy in PH treatment comes from clinical trials conducted in patients with PAH and CTEPH. In a pivotal 12-week RCT in 470 patients with PAH, treprostinil significantly improved exercise tolerance in a dose-related manner and also improved signs and symptoms of PH, haemodynamic parameters, and quality of life compared with placebo.[11] In a long-term, open-label study in 860 participants in RCTs followed for four years, there was a sustained clinical improvement and a 88-70% survival over 1-4 years with SC treprostinil monotherapy.[12] Finally, the improvement in exercise tolerance and New York Heart Association/World Health Organization (NYHA/WHO) functional class was also

reported by a small, long-term, open-label trial in 122 patients, 81% of them with PAH and 19% with inoperable CTEPH, with overall event-free survival rates of 83% and 69% at 1 and 3 years, respectively.[13] Finally, in a recent 24-weeks small RCT enrolling 90 patients with severe, inoperable CTEPH or persistent or recurrent PAH after pulmonary endarterectomy, exercise tolerance improved in patients treated with either low or high doses of SC treprostinil, and beneficial changes were also observed in pulmonary haemodynamic parameters, functional class, and B-type natriuretic peptide (BNP) levels.[14]

The prognosis of the PAH depends on nonmodifiable factors (e.g., clinical subgroup, male gender, and older age) and potentially modifiable characteristics, such as low functional capacity (NYHA/WHO functional class), low exercise capacity (e.g., 6-minute walk distance [6MWD]), haemodynamic parameters indicative of impaired RV function (e.g., low cardiac output or high right atrial pressure), high levels of biomarkers (e.g., BNP), and echocardiographic indices indicative of RV dysfunction (e.g., tricuspid annular plane systolic excursion [TAPSE), right atrial area [RAA], or pericardial effusion).[15] These parameters have been incorporated into routine risk assessment through prediction calculators, which classify patients as low-risk, intermediate-risk, or high-risk categories that determine 1-year mortality risk, can aid in the initial therapeutic choices, and are helpful to monitor disease progression and patients' response to treatment.[1, 15] However, prognosis also depends on RV adaptability and right heart remodelling.[16] Indeed, the RV adapts to increased PH through dilatation to increase contractility and preserve systolic function and normal filling pressures (adaptive remodelling).[17] When this contractility adaptation gets exhausted, the dilated RV leads to decreased systolic function, increased filling pressures, and eventually heart failure (maladaptive remodelling).[17] Both RV systolic dilation and dysfunction are associated with worse PH prognosis, independently of the clinical picture and could represent a risk tool in clinical decisions.[16] The reversal of this RV remodelling (RHRR) can be echocardiographically assessed through the reduction in the right atrium area (RA), left ventricular systolic eccentricity index (LVSEI), and RV end-diastolic area (RVEDA).[18] A recent study conducted in patients with idiopathic PAH (most of them on oral monotherapies) showed that the echocardiographically determined RHRR is related to the reduction of PVR, improvement of the cardiac index (CI), NYHA/WHO functional class, and event-free survival.[18] Additionally, RHRR was shown as an independent prognostic factor that improves the power of predictive models based on traditional clinical and haemodynamic parameters.[18] In another study, the likelihood of RHRR and its prognostic value were further described as higher in patients treated with combination regimens with parenteral prostanoids.[19] Finally, in patients with severe non-reversible PAH, there is evidence that triple therapy with a high dose of SC treprostinil is associated with a substantially greater hemodynamic improvement, with increasing RRHR benefit in proportion to PVR reduction (up to 69%).[20] In summary, these studies show that monitoring the improvement or reversal of RV dimensions could be useful in evaluating RV performance.

Despite more than 15 years of experience in clinical practice with the use of prostanoids in Argentina, real-world data on its use in PH are scarce, and there are no reports on its effect on RV adaptability and RHRR. The primary aim of the TREPAR-HP study is to investigate the long-term effects of SC treprostinil in terms of RHRR in Argentinian patients with PAH or CETPH. In addition, the study will evaluate the impact of clinical events and RHRR on the prognosis of the disease in relation to the treatment and the drug dose. Moreover, it will investigate the effect of SC treprostinil on the reduction of PVR, changes in RV systolic function, morbidity and mortality, quality of life (QoL), and the overall safety and tolerability of this prostacyclin analogue.

METHODS

Design and setting

The study was designed as a national, multicentre, prospective, observational, phase IV study. About 15 specialised centres from Argentina will participate in the trial to recruit approximately 100 patients. As a real-life, pragmatic approach, the study will be conducted in parallel with patients' standard management and treatment in each centre. Therefore, there will be no specific protocol visits, and participants will continue with their usual clinical consultations (including virtual meetings if required) and routine and complementary examinations.

The established recruitment period will open in May 2021, and the study will last 48 months, with an estimated 24-months inclusion period and a minimum follow-up of 24 months (end of the study) from the day of the initiation of treatment with SC treprostinil (day 1). Patients who discontinue early for any reason will undergo a final evaluation before the end of the study.

Eligibility criteria of the TREPAR-HP study

Inclusion criteria

Age >16 years on the date of the informed consent signing. Haemodynamic diagnosis of precapillary PH, confirmed by RHC performed within 6 months prior to the start of the infusion of treprostinil, namely mPAP>20 mm Hg, PVR≥3 WU, and PAWP≤15 mm Hg. PH clinically classified as Group 1 or 4: Group 1 or PAH: Idiopathic, heritable, induced by drugs, toxins, or radiation. Associated with connective tissue diseases or HIV infection. Portal hypertension, congenital heart

disease: simple (atrial septal defect, ventricular septal defect, and patent ductus arteriosus) or with surgical repair. Porto pulmonary hypertension. Group 4 or CTEPH: Chronic thromboembolic pulmonary hypertension. Indication for SC treprostinil administration, initiated prior to the patient's enrolment in the study, and prescribed independently from this protocol. Baseline Doppler echocardiogram (prior to starting treatment with SC treprostinil) with quantification of parameters indicative of right cavities remodelling. Signed informed consent.

Exclusion criteria

Concomitant disease that limits life expectancy (<12 months) or physical-mental disorders that limit follow-up. Active treatment with prostanoids different from SC Treprostinil, PH groups 2, 3 or 5. Kidney failure on dialysis, hepatic failure (Child-Pugh score B or C), or active cancer. Active treatment with another investigational drug. Hypersensitivity to treprostinil. Moderate to severe left valvular disease. Left ventricular ejection fraction ≤40%.

Objectives

The primary objective is the long-term assessment of changes from baseline in echocardiographic parameters indicative of RHRR in patients with a confirmed diagnosis of PAH (Group 1) or CTEPH (group 4) under treatment with SC treprostinil.

Secondary objectives are: to determine the prognostic value of parameters indicative of RHRR and the rate of clinical events regarding treatment and dosage of SC treprostinil. To quantify the impact of the treatment with SC treprostinil on the reduction of PVR with respect to baseline through RHC parameters. To assess whether treatment with SC treprostinil improves RV systolic function with respect to baseline. To evaluate morbidity and all-cause mortality during the follow-up. To assess the patient's QoL after treatment initiation with SC treprostinil. To evaluate the safety and tolerability of SC treprostinil through the incidence of adverse events (AEs).

Study population

Subjects who meet all the inclusion criteria and have no exclusion criteria will be prospectively included in the study.

Outcomes

Primary outcomes and variables

Echocardiographic analyses to assess RHRR will be performed under basal conditions using the commercially available equipment at each institution (e.g., Vivid, GE, or Esaote). They will be conducted in the standard views, with M-mode, 2-dimensional colour flow, and pulsed/continuous-wave Doppler techniques. According to international guidelines for echocardiographic assessment of the right heart in adults, measurements will be obtained with the mean of three consecutive beats.[21] The parameters to be recorded through Doppler echocardiography are summarised.

RHRR will be defined as an echocardiographic decrease in RAA, RV end-diastolic area (REVDA), and left ventricular eccentricity index (LV-EI), and considered as present if one of these three variables is reported.

Secondary outcomes and variables

Disease prognosis will be evaluated using the score obtained from the Registry to Evaluate Early and Long-Term PAH Disease Management (REVEAL) risk calculator, version 2.0 Lite.[22] This tool uses only six modifiable and non-invasive variables (NHYA/WHO functional class, functional class, 6MWD, BNP/NT-proBNP, and renal insufficiency) to classify patients as low, intermediate, and high risk of 1-year mortality.

Improvement in RV systolic function will be defined as a prospective increase of ≥3% in the RV fractional area change (RVFAC) and/or the RV free wall strain rate (RVFW-SR) parameters of the echocardiographic evaluation.

The impact of the treatment with SC treprostinil on the reduction of PVR with respect to baseline will be assessed through the acquired RHC measurements. Catheterisation will be conducted using following the procedures recommended in clinical guidelines. The haemodynamic parameters to be recorded by the RHC are summarised.

The potential changes in the patient's QoL will be measured through the Spanish validated version of the Minnesota Living with Heart Failure (MLHF) questionnaire.[23] This self-administered instrument evaluates the impact of the disease on physical, socio-economic, and psychological aspects of daily life through 21 items and two dimensions (physical and emotional).

To evaluate the morbidity associated with the SC treprostinil treatment, the following events will be considered during the follow-up: 1) development of RV failure requiring hospitalisation or IV diuretic treatment; 2) recurrent syncope; 3) use of IV prostanoids; 4) lung transplant and/or septostomy; and 5) worsening of PH, defined as a progression from NYAH/WHO I-II to III-IV functional class or decrease ≥15% from baseline in 6MWP confirmed in two tests within 14 days (plus additional treatment if already in III-IV functional class). Mortality will be assessed through the rates of all deaths during follow-up regardless of the cause (all-cause mortality).

The safety and tolerability of the treatment with SC treprostinil will be evaluated based on the incidence of AEs, with particular attention to the following potential reactions: injection site pain or inflammation, diarrhoea, headache, jaw pain, flushing, generalised pain, leg oedema, vasodilation, nausea, and thrombocytopenia.

Study procedures

The scheduled follow-ups are presented in Table 3. The baseline evaluation will include data from the RHC haemodynamic assessment, clinical symptoms, PH functional classification, Doppler echocardiographic findings, treatment information, safety and tolerability, and QoL. Data on RHC and QoL will be retrieved every 12 months until the end of the study if available (i.e., after 12 and 24 months after treatment initiation), while all other data and information will be extracted every 6 months (i.e., at 6, 12, 24, and 30 months after treatment initiation). The safety evaluation data will be collected directly after the patient's assessment at each time point of the study (primary data source).

Study medication

Treprostinil (ATC code: B01AC21) is a prostacyclin analogue that exerts direct vasodilation of pulmonary and systemic arterial vascular beds and inhibits platelet aggregation. The commercial treprostinil available in Argentina will be used and administered according to the approved package insert. Patients will receive SC treprostinil according to the indication and judgement of each investigator, independently of this study, and initiated within 12 months of the subject's inclusion in the register. The initial dose of SC treprostinil will be recorded at the first and third month of treatment initiation and then every 6 months, together with the reason for treatment discontinuation, if applicable.

Data extraction and management

All real-life data will be extracted from information available in the original records (or certified copies) of clinical findings, observations, and other activities necessary to reconstruct and evaluate the patient's medical history.

These include hospital records, clinical and administrative briefs, laboratory reports, diaries, evaluation checklists, pharmacy registries, data automatically recorded by existing equipment, microfiches, photographic negatives, microfilms or magnetic media, X-ray reports, subject's records, and files kept in the pharmacy, laboratories or the medical-technical offices involved in the clinical study. A central imaging committee composed of cardiologists specialised in imaging techniques will interpret and quantify the patient's ultrasounds according to an echocardiography manual prepared for the study.

The investigator will complete and sign a web-based electronic case report form (eCRF) for each recruited subject. Data on each participant will be anonymised using only ID numbers, all data will be protected, and passwords will be provided to single users.

Statistical analysis

Sample size calculation

We propose to study a minimum sample size of 90 patients to ensure stability in the prediction models. Considering the scenario of the lowest incidence of combined events at 1 year and 2.5 years (12% and 30%, respectively), we will be able to analyse multiple predictive variables according to the number of events. The proposed hypothesis is that <10% of patients with risk variables and negative remodelling will present a combined event. A 2-tailed alternative hypothesis was used to determine the association between variables and events. The significance limit was established at an α value <5% ($p<0.05$) and $p<0.2$ for the selection of variables for the multivariate model.

Analysis plan

For the primary objective, the analysis will include patients who have baseline data and post-baseline measures for the primary RHRR endpoints. An interim analysis will be performed when 50 patients have evaluation data available to assess this primary objective.

Qualitative variables will be presented as number and percentage (%) and quantitative variables (according to the normality of the distribution) as means with standard deviation (SD) or median with interquartile range (IQR). Depending on the distribution and characteristics of the data, inferential univariate tests will be conducted using the chi-square test, t-test, Wilcoxon test, or Mann Whitney test. Multivariate tests will be analysed through linear regression (simple or multiple) or regression logistics. The Cox model and Kaplan-Meier method will be used for survival analysis.

The change from baseline in RHRR parameters will be assessed using covariance (ANCOVA) analysis with a factor for other PAH-specific therapies (none, before inclusion, or initiated at baseline) and a covariate for baseline RH systolic function.

The change and the associated 95% confidence intervals (CI) will be estimated based on the appropriate model. The ROC curve will be used to identify the optimal cut-off points for the RAA, RVE-DA, and LVSEI variables.

The Cox proportional hazards ratio will be used to estimate the risk to determine the weighted values of the echocardiographic parameters.

All data will be analysed using the IBM SPSS V.14 software (SPSS). The level of statistical significance will be set at alpha <0.05.

Research ethics approval

This observational study will be conducted in accordance with the Declaration of Helsinki of 1975 (in its most recently amended version) and current and local/regional and international regulations applicable to observational studies (including but not limited to Resolution 1480/11 of the Ministry of Health of Argentina).[24]

The trial is registered in the accessible public database Sistema Integrado de Información Sanitaria Argentino (SISA; https://sisa.msal.gov.ar/sisa/#sisa), Registro Nacional de Investigaciones en Salud (RENIS), trial number IS003303.

Consent

Prior to inclusion, all patients will receive verbal and written information about the study aims, procedures and potential risks during the study and will be asked to sign a written informed consent before entering the study registry. Participation in the study will be voluntary, and patients will be able to withdraw at any time without any consequences.

Doppler echocardiographic parameters and right heart catheterisation that will be recorded for each patient

Doppler echocardiography

RAA: right atrial area (cm^2), RVE-DA: right ventricular end-diastolic area (mm), LV-EI: left ventricular end-diastolic and end-systolic eccentricity index, TAPSE: tricuspid annular plane systolic excursion (mm), RVFAC: change in right ventricular fractional area change (%), RVFW-SR: right ventricle free wall strain rate (%) , LVEF: left ventricle ejection fraction, TRV: Tricuspid regurgitation velocity (m/sec), IVC (inferior vena cava) diameter (mm), IVC collapse (collapsibility index), RV systolic dysfunction (mild, moderate, or severe) and pericardial effusion (no effusion, minimum, or more than minimum).

RH catheterisation

Heart rate per minute, RAP: right atrial pressure (mm Hg), mPAP: mean systolic and diastolic pulmonary artery pressure (mm Hg), CO: cardiac output (L/min), CI: cardiac index ($L/min/m^2$), PAWP: pulmonary capillary wedge pressure (mm Hg), PaO_2: arterial oxygen saturation (%). PVR: pulmonary vascular resistance (Wood units), calculated with the formula PVR=(mPAP-PAWP)/CO.

Table 1: Chart of study procedures and data to be collected from the patient's medical records.

Variables	Study period			
	Baseline	Every 6 months	Every 12 months	Month 48 or end of study
Recruitment	X			
Baseline demographic data (age, sex, and social security coverage)	X			
Diagnostic classification (PAH or CETPH)	X			
Right heart catheterisation	X		X[1]	X[2]
Review of inclusion and exclusion criteria	X			
Informed consent	X			
Clinical and functional assessment	X	X	X	X
Vital signs (pulse rate and SBP)	X	X	X	X
NYHA/WHO functional class (I to IV)	X	X	X	X
6MWT: Distance, Modified Borg dyspnea scale, Initial and final SaO_2, Initial, final, and after 1 min recuperation pulse rate and Predicted distance equation	X	X	X	X
Progression of symptoms. Disease progression (no progression; slow progression; or rapid progression)	X	X	X	X

Continued.

Variables	Study period			
	Baseline	Every 6 months	Every 12 months	Month 48 or end of study
Presence of syncope*	X	X	X	X
Presence of right heart failure**	X	X	X	X
Angina Pectoris and atrial fibrillation/flutter	X	X	X	X
Laboratory parameters, Creatinine, NT-probing/BNP and Troponin I	X	X	X	X
Doppler echocardiogram	X	X	X	X
Treatment				
Treprostinil dose (initial, at 1st, 3rd, and afterwards every 6 months) and reason for discontinuation	X	X	X	X
HP-specific medication† (start date, end date, and reason for suspension)	X	X	X	X
Concomitant chronic medication	X	X	X	X
Adverse events	X	X	X	X
Quality of life (MHLF)	X		X	X

[1]Within 12 months of follow-up and [2]within 30 months if available. *Occasional syncope defined as occurring during a strenuous exercise or occasional orthostatic syncope in an otherwise stable patient. Repetitive syncope defined as syncope episodes even with little or no regular physical activity. **Defined as the presence of two or more of the following signs: jugular ingurgitation, hepatojugular reflex, peripheral oedema hepatomegaly, and ascites. †Including endothelin receptor antagonists (bosentan, macicetan, ambrisentan, or other); phosphodiesterase type 5 (PDE5) inhibitors (sildenafil, taladafil, or other); soluble guanylate cyclase (sGC) stimulators (rociguat); selective prostacyclin (Ip) receptor agonists (selexipag); calcium channel blockers; furosemide; thiazide-type diuretics; aldosterone antagonists; digoxin; vitamin K antagonists, novel oral anticoagulants (NOACs), or other medication. 6MWT, 6-minute walk test; MLHF, Minnesota living with heart failure questionnaire; NT-proBNP, N-terminal pro-b-type natriuretic peptide; SaO_2, oxygen saturation; SBP, systolic blood pressure.

DISCUSSION

The TREPAR-HP real-life, pragmatic study is designed to gather valuable information on the characteristics of patients with PH and the long-term effects of the treatment with SC treprostinil in our geographical region. Although the availability of targeted therapies is lower in Latin America, the survival rates are similar to those reported in Europe or the US.[6] However, Latin American countries have several epidemiological differences compared with other developed countries, as the distribution of PAH forms and the profile of PAH patients differ from other international registries.[6] For instance, most diagnosed patients are young and working age, while studies in Europe or the US patients are ≥50 years at diagnosis.[6] Moreover, the proportion of patients with severe disease (NYHA/WHO functional class III-IV) is lower than in Europe or the US.[6] Additionally, the proportion of PAH patients with congenital heart disease reported in Argentina is higher than in Europe and the US (28% vs <15%).[6] It is therefore necessary to evaluate prognostic scales representing the different populations in Latin America.[6] On the one hand, there is little prospective information regarding risk variables and prognostic factors referred by international PH clinical guidelines in this population, the current risk scores have not been validated, and its impact on free-event survival is still unknown.[25] On the other hand, although SC treprostinil is widely used in Latin America and represents a good option to address these knowledge gaps, there is limited evidence on its clinical benefits and long-term effects, in particular when used at high doses, and there is even less available information on its impact in RV remodelling. The need to address not only vasoconstriction but also vascular remodelling in studies assessing therapeutic interventions in PAH has been recently highlighted.[26] The incorporation of RRHR echocardiographic indices as endpoints has been pointed out as relevant not only to quantify their association with clinical and haemodynamic parameters but also to evaluate to what extent they have risk assessment and prognostic implications.[26]

Another gap in the knowledge of PAH is the lack of long-term, longitudinal data regarding patient's health-related quality of life (HRQoL), and there are few data on its potential role in the prognosis of the disease.[27, 28] It is well established that symptoms of PAH have a substantial adverse impact on the subject's functional mobility, well-being, and emotional and social functioning.[29] Besides, intolerable adverse reactions associated with PAH therapies such as site infections from intravenous lines or the pain of subcutaneous treatment, the latter reported by approximately 85% of patients and causing long-term

treatment discontinuation in up to 5-23% of subjects,[30] may also impact HRQoL negatively.[31] Of note, an international, self-reported survey found that more than half of patients with PAH stated that the disease had a very significant impact on their daily lives.[32] Considering this, regulatory agencies and clinical guidelines recommend incorporating patient-reported outcome (PRO) instruments in PAH clinical trials.[29] However, there is a need to validate these tools in real-world clinical scenarios. For this reason, the study that we proposed will include the assessment of HRQoL through the MLHF questionnaire as an outcome. One advantage of this instrument is that the reproducibility, validity, responsiveness, and prognostic significance have evaluated in a mixed cohort of patients with PAH and CETPH.[33]

The TREPAR-HP has several strengths. Firstly, the prospective design will minimise potential residual confounding by unmeasured variables, which is a common limitation of retrospective designs, by increasing the accuracy of data collection. Secondly, we aim to obtain patients from different centres across the country, which will provide data coming from real-world clinical practice with SC treprostinil in Argentina. Nonetheless, the results will not only provide valuable country- and region-specific information but will also contribute to the existing global evidence on the efficacy and safety of SC treprostinil. Moreover, it will expand the preliminary experience on the usefulness of long-term RHRR monitoring in determining right heart performance, disease progression, and prognosis. Limitations of the TREPAR-HP study include the open-label observational nature, which prevents drawing causal inferences between right heart remodelling and outcomes. Moreover, the collected data may not be as robust as blinded studies with control groups, but this potential bias will be addressed by external monitoring of all clinical records and independent central analysis of all imaging parameters by experts in cardiac imaging.

CONCLUSIONS

In summary, the results of the TREPAR-PH study will improve our understanding of the long-term evolution of PAH in patients and the impact of SC treprostinil therapy on our geographical region and abroad. It is also anticipated that the results will help to identify echocardiographic parameters helpful in determining the role of right heart remodelling in disease evolution, risk assessment, and survival prediction.

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REFERENCES

1. Galiè N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). Eur Heart J. 2016;37(1):67-119.
2. Lopes AA, Bandeira AP, Flores PC, Santana MV. Pulmonary hypertension in Latin America: pulmonary vascular disease: the global perspective. Chest. 2010;137(6):78s-84s.
3. Lau EMT, Giannoulatou E, Celermajer DS, Humbert M. Epidemiology and treatment of pulmonary arterial hypertension. Nat Rev Cardiol. 2017;14(10):603-14.
4. Echazarreta DF, Perna ER, Coronel ML, Diez M, Lescano AJ, Atamañuk AN, et al. Collaborative registry of pulmonary hypertension in Argentina (RECOPILAR). Final analysis. Medicina (B Aires). 2021;81(2):180-90.
5. Talavera ML, Cáneva JO, Favaloro LE, Klein F, Boughen RP, Bozovich GE, et al. Hipertensión arterial pulmonar. Registro de un centro de referencia en Argentina. Rev Am Med Resp. 2014;14(2):144-52.
6. Valverde AB, Soares JM, Viana KP, Gomes B, Soares C, Souza R. Pulmonary arterial hypertension in Latin America: epidemiological data from local studies. BMC Pulm Med. 2018;18(1):106.
7. Humbert M, Guignabert C, Bonnet S, Dorfmüller P, Klinger JR, Nicolls MR, et al. Pathology and pathobiology of pulmonary hypertension: state of the art and research perspectives. Eur Respir J. 2019;53(1):1801887.
8. Simonneau G, Montani D, Celermajer DS, Denton CP, Gatzoulis MA, Krowka M, et al. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. Eur Respir J. 2019;53(1).
9. Kumar P, Thudium E, Laliberte K, Zaccardelli D, Nelsen A. A Comprehensive Review of Treprostinil Pharmacokinetics via Four Routes of Administration. Clin Pharmacokinet. 2016;55(12):1495-505.
10. Pedersen LM, Kruger M, Grimm D, Infanger M, Wehland M. The prostacyclin analogue treprostinil

in the treatment of pulmonary arterial hypertension. Basic Clin Pharmacol Toxicol; 2019.
11. Simonneau G, Barst RJ, Galie N, Naeije R, Rich S, Bourge RC, et al. Continuous subcutaneous infusion of treprostinil, a prostacyclin analogue, in patients with pulmonary arterial hypertension: a double-blind, randomized, placebo-controlled trial. Am J Respir Crit Care Med. 2002;165(6):800-4.
12. Barst RJ, Galie N, Naeije R, Simonneau G, Jeffs R, Arneson C, et al. Long-term outcome in pulmonary arterial hypertension patients treated with subcutaneous treprostinil. Eur Respir J. 2006;28(6):1195-203.
13. Lang I, Gomez-Sanchez M, Kneussl M, Naeije R, Escribano P, Skoro-Sajer N, et al. Efficacy of long-term subcutaneous treprostinil sodium therapy in pulmonary hypertension. Chest. 2006;129(6):1636-43.
14. Sadushi-Kolici R, Jansa P, Kopec G, Torbicki A, Skoro-Sajer N, Campean IA, et al. Subcutaneous treprostinil for the treatment of severe non-operable chronic thromboembolic pulmonary hypertension (CTREPH): a double-blind, phase 3, randomised controlled trial. Lancet Respir Med. 2019;7(3):239-48.
15. Raina A, Humbert M. Risk assessment in pulmonary arterial hypertension. Eur Respir Rev. 2016;25(142):390.
16. Fine NM, Chen L, Bastiansen PM, Frantz RP, Pellikka PA, Oh JK, et al. Outcome prediction by quantitative right ventricular function assessment in 575 subjects evaluated for pulmonary hypertension. Circ Cardiovasc Imaging. 2013;6(5):711-21.
17. Vonk-Noordegraaf A, Haddad F, Chin KM, Forfia PR, Kawut SM, Lumens J, et al. Right Heart Adaptation to Pulmonary Arterial Hypertension: Physiology and Pathobiology. J Am Coll Cardiol. 2013;62(25):D22-D33.
18. Badagliacca R, Poscia R, Pezzuto B, Papa S, Reali M, Pesce F, et al. Prognostic relevance of right heart reverse remodeling in idiopathic pulmonary arterial hypertension. J Heart Lung Transplant. 2018;37(2):195-205.
19. Badagliacca R, Papa S, Manzi G, Miotti C, Luongo F, Sciomer S, et al. Usefulness of Adding Echocardiography of the Right Heart to Risk-Assessment Scores in Prostanoid-Treated Pulmonary Arterial Hypertension. JACC Cardiovasc Imaging. 2020;13(9):2054-56.
20. D'Alto M, Badagliacca R, Argiento P, Romeo E, Farro A, Papa S, et al. Risk Reduction and Right Heart Reverse Remodeling by Upfront Triple Combination Therapy in Pulmonary Arterial Hypertension. Chest. 2020;157(2):376-83.
21. Rudski LG, Lai WW, Afilalo J, Hua L, Handschumacher MD, Chandrasekaran K, et al. Guidelines for the Echocardiographic Assessment of the Right Heart in Adults: A Report from the American Society of Echocardiography: Endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. J Am Soc Echocardiogr. 2010;23(7):685-713.
22. Benza R, Kanwar M, Raina A, Scott JV, Zhao C, Selej M, et al. Development and Validation of an Abridged Version of the REVEAL 2.0 Risk Score Calculator, REVEAL Lite 2, for Use in Patients With Pulmonary Arterial Hypertension. Chest. 2020;159:337-46.
23. Garin O, Soriano N, Ribera A, Ferrer M, Pont À, Alonso J, et al. Validación de la versión española del Minnesota Living with Heart Failure Questionnaire. Rev Esp Cardiol. 2008;61(3):251-59.
24. Ministerio de Salud. Salud publica. Resolución 1480/2011. Guía para Investigaciones con Seres Humanos. Boletín Oficial de la República Argentina. Available at: https://www.uba.ar/archivossecyt/image/Resolucion1480-11%20Naci%C3%B3n.pdf Accessed on 12 August 2021.
25. Lescano A, Damianich G, Crippa D, Besmalinovich E, Farina J, Fernández I, et al. Factores pronósticos en hipertensión pulmonar: Nuestra experiencia. Insuf Card. 2018;13(2):51-6.
26. Farmakis IT, Demerouti E, Karyofyllis P, Karatasakis G, Stratinaki M, Tsiapras D, et al. Echocardiography in Pulmonary Arterial Hypertension: Is It Time to Reconsider Its Prognostic Utility? J Clin Med. 2021;10(13).
27. Yorke J, Deaton C, Campbell M, McGowen L, Sephton P, Kiely DG, et al. Symptom severity and its effect on health-related quality of life over time in patients with pulmonary hypertension: a multisite longitudinal cohort study. BMJ Open Respir Res. 2018;5(1):e000263.
28. Mathai SC, Suber T, Khair RM, Kolb TM, Damico RL, Hassoun PM. Health-related Quality of Life and Survival in Pulmonary Arterial Hypertension. Ann Am Thorac Soc. 2016;13(1):31-9.
29. Levine DJ. Pulmonary arterial hypertension: updates in epidemiology and evaluation of patients. Am J Manag Care. 2021;27(3):S35-S41.
30. Mathier MA, McDevitt S, Saggar R. Subcutaneous treprostinil in pulmonary arterial hypertension: Practical considerations. J Heart Lung Transplant. 2010;29(11):1210-7.
31. Delcroix M, Howard L. Pulmonary arterial hypertension: the burden of disease and impact on quality of life. Eur Respir Rev. 2015;24(138):621-9.
32. Ferrari P, Armstrong I, Aldrighetti R, Howard L, Ryftenius H, Fischer A, et al. Impact of pulmonary arterial hypertension (PAH) on the lives of patients and carers. Eur Respir J. 2013;42(57):P2631.
33. Cenedese E, Speich R, Dorschner L, Ulrich S, Maggiorini M, Jenni R, et al. Measurement of quality of life in pulmonary hypertension and its significance. Eur Respir J. 2006;28(4):808.

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