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Early View

Research letter

Survival of schistosomiasis-associated pulmonary arterial hypertension in the modern management era

Caio Julio Cesar Fernandes, Bruna Piloto, Marcela Castro, Francisca Gavilanes Oleas, Jose Leonidas Alves Jr, Luis Felipe Lopes Prada, Carlos Jardim, Rogerio Souza

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Survival of schistosomiasis-associated pulmonary arterial hypertension in the modern management era

Caio Julio Cesar Fernandes

Bruna Piloto

Marcela Castro

Francisca Gavilanes Oleas

Jose Leonidas Alves-Jr

Luis Felipe Lopes Prada

Carlos Jardim

Rogerio Souza

Pulmonary Division – Heart Institute – University of Sao Paulo Medical School – Sao Paulo - Brazil

Address for correspondence

Rogerio Souza, MD, PhD

Pulmonary Department – Heart Institute

University of Sao Paulo Medical School

Av. Dr. Eneas de Carvalho Aguiar, 44 - Sao Paulo – Brazil - 05403-000

souza.rogerio@me.com

Tel/Fax: +55 11 26 61 56 95

Background:

Pulmonary arterial hypertension (PAH) is a life-threatening disease characterized by an elevated pulmonary vascular resistance in the absence of left ventricular disease, increasing pulmonary artery pressure, with consequent right ventricular failure and death (1). Several etiologies have been associated to PAH, including connective tissue diseases, congenital heart diseases and chronic infections, such as HIV. Due to its high prevalence in developing countries, one of the most relevant forms of PAH worldwide is the one associated to schistosomiasis (2).

Schistosomiasis associated pulmonary arterial hypertension (Sch-PAH) is present in 5% of patients with the hepatosplenic form of the disease (3). Due to its histological and hemodynamic similarities to idiopathic PAH (IPAH), it is classified within group 1 (pre-capillary pulmonary hypertension) of the current pulmonary hypertension classification (4). However, despite the similarities, a previous cohort has shown that Sch-PAH has a distinct, more benign course than IPAH, even in the absence of specific therapy (5).

Data regarding the efficacy of specific PAH therapy in Sch-PAH are scarce. Improvements in functional class, cardiac output and six minute walking test distance (6MWT), using phosphodiesterase-5 inhibitors (PDE5i) or endothelin 1 receptor antagonists (ERA) were demonstrated in a small cohort of 12 SCH-PAH patients (6). The effect of PAH treatment on hard-end points, such as clinical worsening or survival, has not been evaluated in this population, until this date.

The aim of this study was to compare the survival of newly diagnosed Sch-PAH patients treated with PAH targeted therapies against a group of untreated patients from a historical cohort.

Methods:

Data from all consecutive, newly diagnosed Sch-PAH patients referred to our center in Brazil were analyzed. Sch-PAH was characterized by the presence of mean pulmonary arterial pressure ≥ 25mmHg with pulmonary artery occlusion pressure ≤ 15mmHg, in the absence of significant lung parenchymal disease, left ventricular dysfunction or chronic thromboembolic disease, associated with the presence of periportal fibrosis and/or left liver lobe enlargement associated with at least one of the following features: positive epidemiology, previous treatment of schistosomiasis or identification of eggs in stool or rectal biopsy(7). Since specific PAH therapy became widely available in Brazil after 2010, patients diagnosed before this date received only supportive therapy and comprised our historical cohort. After 2010, Sch-PAH patients were regularly treated with PDE5i, ERA or both, at discretion of the attending physician, in accordance to the available guidelines (8, 9).

Baseline clinical, demographical, including New York Heart Association (NYHA) functional class (FC) assessment, 6-min walk test distance (6MWT), brain natriuretic peptide (BNP) and hemodynamic data were collected.

Analysis was performed using the SPSS 21 statistical package (SPSS, Inc). All continuous variables are expressed as mean $\pm$ SD and compared using Student t test. Categorical data are presented as proportions and compared using chi-square or Fisher exact test, as appropriate.

The 60-month survival was evaluated using Kaplan-Meier estimate. Log-rank test was used for curve comparison. A P value < 0.05 was considered statistically significant.

Results:

The study population comprised 102 Sch-PAH patients; 50 patients (49%) were diagnosed before 2010 and, therefore, did not receive specific PAH therapy (untreated group – historic control). Except for the availability of specific treatment, there was no change in the standard of care during the whole observation period. Fifty-two patients (51%) were diagnosed after 2010 and received targeted therapies: 41 patients (40.2%) received monotherapy with PDE5i, 10 patients (9.8%) received monotherapy with ERA, and 1 patient (1%) received upfront combination therapy.

Sch-PAH untreated and treated patients had similar baseline clinical and demographic data. At diagnosis, the mean age was 53.7±13.2 vs. 52.7±13.0 years, 6MWT was 458±149m vs. 411±100m, BNP was 107±90 vs. 142±183pg/dL. Among untreated patients, there was 68% of female patients, with 25 patients (55%) in FC I-II and 20 patients (45%) in FC III-IV, whilst in the treated group, 59.6% of female patients, with 26 patients (51%) in FC I-II and 25 patients (49%) in FC III-IV ($p>0.05$ for all comparisons).

The hemodynamic impairment was also similar between groups. Untreated and treated patients presented right atrium pressure of 9.7±4.7 and 10.8±5.7 mmHg ($p=0.281$); mean pulmonary arterial pressure of 52.4±16.7 vs. 59.9±17.9 mmHg ($p=0.033$), pulmonary artery occlusion pressure of 11.7±4.1 vs. 13.4±5.4 mmHg ($p=0.085$), cardiac output of 4.8±1.6 vs. 4.4±1.4 L/min ($p=0.208$) and pulmonary vascular resistance of 10.1±7.1 vs. 11.8±6.4 WU ($p=0.225$), respectively. No statistically significant difference was found between the groups. None of the patients presented acute vasodilator response, regardless of the group (10).

The survival rate of the untreated group at 60 months was 69.2% for the untreated and 89.1% for the treated Sch-PAH patients ($p=0.029$) (figure 1).

Discussion:

The use of specific PAH therapy in Sch-PAH patients was associated with improved survival, in comparison with a historical control group of untreated patients. To our knowledge, this is the first time that this information is reported in medical literature.

Schistosomiasis is the third most prevalent form of chronic infection disease worldwide, possibly infecting 200 million people (11). Considering the prevalence of 5% of PAH in patients with the hepatosplenic form of the disease (3), Sch-PAH is clearly one of the most relevant forms of PAH, particularly in developing countries (12, 13). Nevertheless, this population is rarely included in the large trials evaluating PAH targeted therapies (14). Despite that, current PAH guideline recommends specific treatment for schistosomiasis, in line with other entities included in group 1 of the current PH classification(9). However, the long-term efficacy of PAH targeted therapies had never been demonstrated in Sch-PAH.

Our study has some limitations that need to be highlighted. It is a non-randomized single center study, using historical controls as comparators, thus limiting the availability of follow-up data regarding the effect of targeted therapies in the functional and hemodynamic variables. However, our center is the largest referral center in the country, receiving patients from all

other regions, including those from highly endemic areas. Furthermore, survival of untreated Sch-PAH survival rate was consistent with previously published data (5, 15). Likewise, the better survival associated with treatment is in line with the clinical and hemodynamic benefits of targeted PAH therapy in Sch-PAH previously demonstrated (6).

In conclusion, our results provide more robust evidence supporting current PAH guidelines recommendation, reinforcing the indication for targeted therapies in Sch-PAH, similarly to other forms of PAH.

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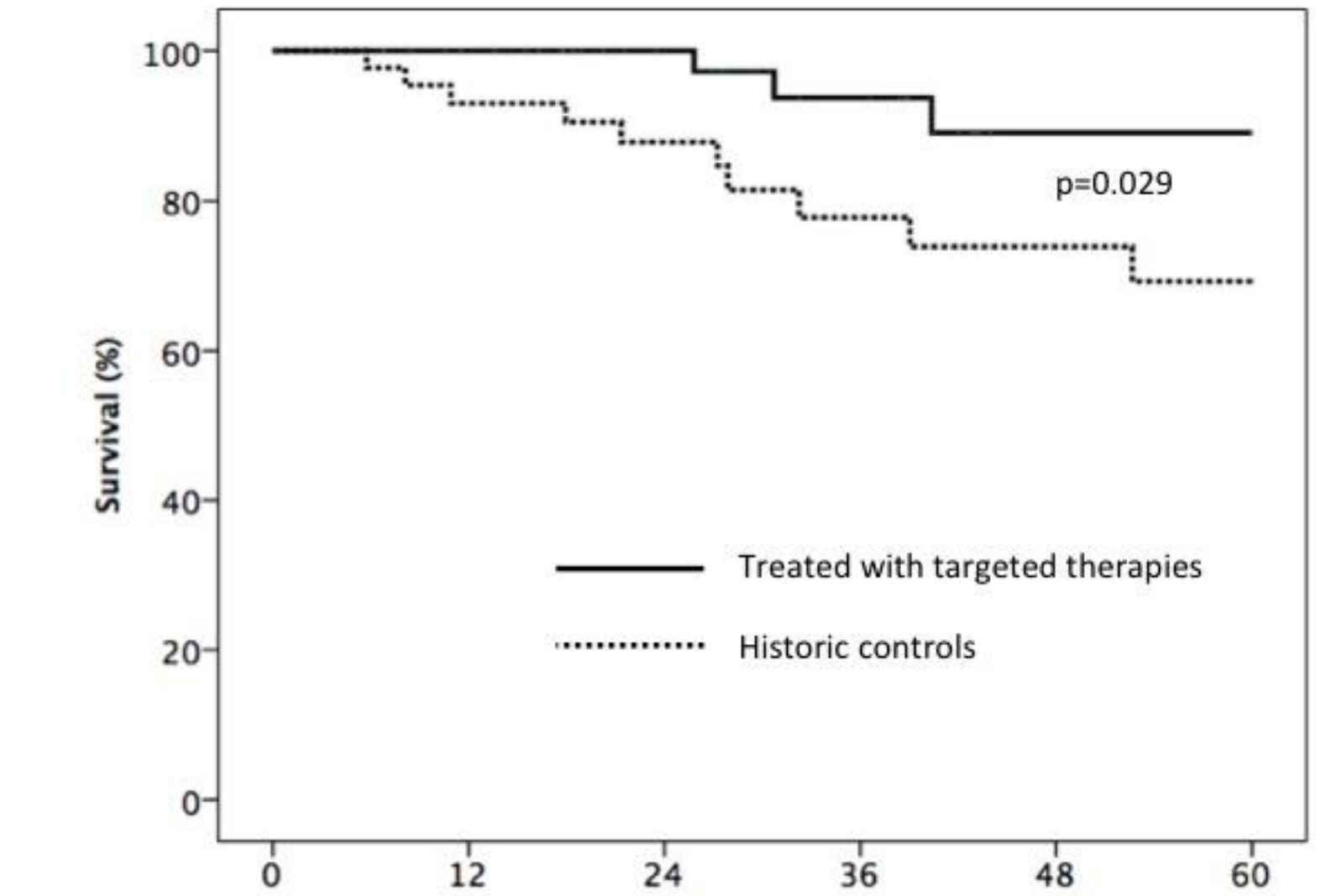
Figure 1. Survival of Sch-PAH according to treatment



No. at risk						
Treated	52	46	36	26	13	13
Untreated	50	38	30	20	16	15