Clinical and Echocardiographic Characteristics After Six Months of Sacubitril Valsartan in Chagas Heart Disease.

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What is already known about this subject:

Chagas cardiomyopathy is a chronic pathology responsible for high rates of morbidity and lethality, in addition to having a relevant social impact. Currently, its treatment is based on medications used to treat heart failure, and there are few studies that have tested these medications in this population, usually with small samples and limited statistical power. So far, the efficacy and safety of using sacubitril valsartan in this population has not been evaluated in clinical trials.

What this study adds:

This study was carried out in a hospital in the Northeast of Brazil, a reference in the treatment of patients with Chagas heart disease, mainly because it is located in an endemic region of Chagas disease. A multidisciplinary team followed a cohort of patients who received sacubitril valsartan for at least six months, providing data on the safety and efficacy of this drug.

Abstract

Chagas cardiomyopathy is the most prevalent non-ischemic cardiomyopathy in Latin America, with high morbidity and mortality even today. Treatment of these patients is based on the use of medications for heart failure. This study evaluated a cohort of patients with Chagas heart disease who used sacubitril valsartan at a referral hospital for the disease in Brazil. After six months, there was a symptomatic improvement in these individuals assessed by the NYHA classification, with a 44.3% reduction in the absolute number of patients classified as III-IV in the period (p 0.035), but without changes in the parameters on the echocardiogram for reverse ventricular remodeling and still high mortality rate and hospitalization. These results emphasize the importance of studying the use of sacubitril valsartan in chagas heart disease to better describe its effectiveness taking into account the peculiarities of these individuals

Introduction

Chagas heart disease (ChHD) is a chronic pathology associated with high rates of morbidity and lethality, in addition to a relevant social impact. ChHD has a worse prognosis when compared to other causes of dilated cardiomyopathies mainly due to its etiopathogenesis and more significant ventricular remodeling [1,2]. Two-year mortality can reach 50-80%, especially among individuals with more severe presentations of the disease [3,4]. Despite its severity and peculiarities, even today its treatment is based on extrapolating the efficacy of the drugs commonly used for heart failure (HF). Some previous studies have evaluated the use of these drugs in Chagas cardiomyopathy, however with small samples and limited statistical power [5,6].

Angiotensin receptor neprilysin inhibitor (ARNI), represented by sacubitril valsartan, has been shown to be effective in reducing the risks of death and hospitalization due to HF [7]. However, few studies have evaluated its use in patients with ChHD and there is not much information about its effectiveness and safety in this population. The aim of this study was to describe a cohort of patients diagnosed with ChHD who had used ARNI for at least six months and to report whether there were any clinical and echocardiographic changes during treatment with the drug.

Methods

Prospective and observational cohort from a single center, at Ana Nery Hospital. This hospital is a reference in the treatment of Chagas cardiomyopathy because it is located in an endemic area of the disease in Northeastern Brazil. The research was based on database analysis and review of medical records.

Study population

Eligibility requirements included patients diagnosed with ChHD, confirmed by serology (ELISA and IFI), with left ventricular ejection fraction (LVEF) $\leq$ 40%, who used sacubitril valsartan for at least six months. These patients were identified through the hospital's drug dispensing list between May 2017 and February 2020. Exclusion criteria were refusal to take medication and implantation of a cardiac implantable electronic device during the study period.

According to resolution 466/2012 of the National Health Council, the present study was approved by the local research ethics committee, and all procedures were performed in accordance with the declaration of Helsinki.

Data collect

The data were collected through the electronic medical record and through a specific document filled in periodically (monthly by telephone and in person every six months) by a multiprofessional HF team responsible for the prescription of ARNI; this team selected and followed up the patients for this program after clinical and social evaluation.

Demographic and clinical characteristics, clinical outcomes, data from transthoracic echocardiogram and laboratory tests were collected before and after a minimum period of six months with sacubitril valsartan. Although there is no standardized definition for left ventricular reverse remodeling (LVRR) [8], this study considered that the observation of an increase in LVEF concomitantly with reductions in left ventricular systolic diameter (LVSD) and left ventricular diastolic diameter (LVDD) would be indicative of LVRR.

Study Outcomes

The primary outcome was to assess symptomatic improvement through the New York Heart Association (NYHA) classification and the occurrence of LVRR in these patients after at least six months of using sacubitril valsartan.

Statistical Analysis

Categorical variables were described as frequencies and percentages. The Kolmogorov-Smirnov test was used to verify the normal distribution of continuous variables. Variables with normal distribution were described by means and standard deviations and compared using Student's t test. Variables with non-normal distribution were described by the medians and interquartile ranges 25% and 75%, and compared using the Wilcoxon test. A value of $P < 0.05$ was considered to be statistically significant. The Statistical Package for the Social Sciences (SPSS) version 20.0 was used for the analysis of all data. The data were analyzed using IBM SPSS Statistical Package v.21 (IBM Corporation, Armonk, NY).

Results

This study evaluated 19 patients with Chagas cardiomyopathy who started sacubitril valsartan. Two patients died before completing six months of medication, and it was not possible to prospectively analyze their clinical and echocardiographic data. Two other patients died after the six-month follow-up clinical evaluation, but did not repeat the echocardiogram, thus they were excluded from the comparative analysis of the data from this exam.

The baseline characteristics of the patients are shown in Table 1. The majority (63.1%) were women and the median age was 58 years (IQ 42.75 - 62.25), with 9 (47.4%) patients having hypertension, 3 (15.8%) diabetes and 8 (42.1%) previous stroke. Symptoms of HF by NYHA were class III-IV in 73.7% of individuals. In the initial prescription, six individuals (31.6%) used angiotensin receptor blocker (ARB) and thirteen (68.4%) angiotensin-converting enzyme inhibitor (ACEI), all were using beta-blockers (BB) and spironolactone. Seventeen (89.5%) patients used furosemide, with a median dose of 80 mg. The majority (78.9%) were considered to have medical therapy optimized for HF before the introduction of ARNI. Considering the echocardiographic data, the initial mean LVEF was 30.8% (± 8.3) and the mean of the LVSD and LVDD were 55.5 mm (± 8.6) and 65.1 mm (± 8.5), respectively.

In the follow-up of the 17 patients who used sacubitril valsartan for at least six months, only 35.3% of them reached the maximum dose. Median SBP was 95 mmHg (IQ 77.5 - 118.5) and there were few episodes of symptomatic hypotension, but without the need to discontinue it. Twelve (70.6%) individuals were considered NYHA class I-II and 94.1% were taking furosemide with a median dose of 80 mg. The comparative analysis of medians of symptoms by NYHA class at admission and after at least six months with ARNI showed significant improvement among these patients (p 0.035) (Figure 1). Of the total amount of patients, nine (47.4%) were hospitalized for decompensated HF and six (31.6%) died with the progression of the disease.

The analysis of echocardiographic data after six months of medication showed an average LVEF of 31.8% (± 12.5) with mean LVSD and LVDD of 55.4 mm (± 11.9) and 66.3 (± 9.3) mm, respectively (Table 2). Taking into account the criteria used by the current study to consider LVRR, only four (26.7%) patients had this outcome.

Discussion

In this cohort of patients with Chagas cardiomyopathy treated with sacubitril valsartan for at least six months, there was a significant improvement in the symptoms. Prior to ANRI, 73.7% of patients were classified as NYHA III-IV and, after six months of medication, this number dropped to 29.4%. On the other hand, echocardiographic data showed no improvement in the parameters of reverse ventricular remodeling. During this period, high rates of hospitalization for HF decompensation (47.4% of cases) and of mortality (31.6% of cases) were observed, probably due to the greater severity and worse prognosis of these patients already at the time of the introduction of sacubitril valsartan. It is worth mentioning that the majority of patients were considered with medical therapy optimized for HF with the maximum tolerated dose and that all patients were using ACE inhibitors or BRA, BB and spironolactone before the introduction of ARNI.

ChHD leads to more severe heart disease and worse clinical management, which can be justified by the persistence of chronic inflammation in myocytes, dysregulation of cardiac autonomic innervation and greater ventricular remodeling [9]. Despite this, the treatment of patients with ChHD follows the same logic as the treatment of HF by other etiologies through the inhibition of the renin-angiotensin-aldosterone system and the adrenergic system. Dávila et al showed that metoprolol was related to symptomatic improvement, increased LVEF and reduced ventricular diameters in patients with ChHD after ten weeks [10]. A single-centered Brazilian study evaluated 42 patients with Chagas cardiomyopathy using ACE inhibitors and spironolactone, and noted that there was a reduction in LVSD, an increase in LVEF in patients with initial LVEF ≤45%, improvement in quality of life questionnaires and reductions in BNP. These patients were subsequently randomized to carvedilol or placebo, and, after a period of four months, there was an increase in LVEF in the carvedilol group, but without symptomatic improvement [11].

Sacubitril valsartan has been poorly studied in Chagas cardiomyopathy. In PARADIGM-HF, only 113 individuals (0.012%) had ChHD, which limits the conclusion about the clinical benefit in this population [7,12,13]. To date, there are no published studies on the use of this medication in the ChHD, which shows the urgency

to assess the effects of ARNI in these individuals, considering the severity of these patients and the benefits of this medication.

The medications classically used in the treatment of HF have already been shown to have an impact on LVRR, by reducing LV volumes and increasing LVEF, with a consequent improvement in prognosis [14,15]. Sacubitril valsartan also acts in the LVRR process with a consequent reduction in unfavorable clinical outcomes [16–19]. In ChHD, few studies have evaluated the impact of LVRR on the prognosis of these patients [20,21]. A retrospective Brazilian cohort followed 159 individuals with Chagasic cardiomyopathy for ten years and observed that 25% of them evolved with LVRR (defined by a reduction in LVDD and an increase in LVEF) with triple therapy, however there was no difference in outcomes such as hospitalization for HF, need of transplantation and cardiogenic shock when compared to the other patients [4].

The current study found no significant LVRR in patients with ChHD on ARNI for six months. This finding is probably related to the selection of more severe patients by the hospital's multidisciplinary team to start the medication. Baseline characteristics show a high incidence of malnutrition, a median of the MAGGIC score of 22, with the majority (63.1%) having been hospitalized in the last year and with initial echocardiographic parameters already considerably severe. The severity of these patients is evident when observing that despite the good adherence of therapy with BB, spironolactone and sacubitril valsartan in the follow-up, many evolved with poor clinical outcomes in a short period, with 47.4% being hospitalized for worsening HF and 31.6% evolving to death. Perhaps the greatest benefits with the use of sacubitril valsartan are not achieved when it is introduced in late stages of HF by Chagas heart disease.

Despite the small sample, this study brings its contribution by showing a scenario of the use of sacubitril valsartan in ChHD in the real world, describing the occurrence of symptomatic improvement in these individuals, information about the safety and tolerability of this drug and about the inexpressive efficacy in echocardiographic parameters during the follow-up. As a reference hospital for the treatment of HF in the Brazilian public health system, our patients have wide access to all therapies indicated by the current guidelines, including the use of sacubitril valsartan, and yet there is a high rate of unfavorable outcomes. This leads to a reflection about the

high morbity and mortality from ChHD in the real world and the need for further studies to assess the peculiarities of this population.

It is worth highlighting some limitations of the study. The collection of clinical and echocardiographic information through medical records and the multidisciplinary team form has a deficiency inherent in the method itself. The analysis of the echocardiogram data has certain fragility, since the data are heterogeneous because they are performed by different operators on different devices. The use of ventricular diameters to define LVRR is also questionable, but we chose to use these parameters because they are more easily available in the records and because it has already been done by other studies.

In this cohort of patients with ChHD using sacubitril valsartan for a minimum period of six months, a significant symptomatic improvement was observed that coincides with the introduction of the medication. There was no improvement in echocardiographic data and the mortality rate and new hospitalizations for HF were high. Further studies are needed to understand the clinical benefit of ARNI in Chagas cardiomyopathy.

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Conflict of interest statement

The Authors declare that there is no conflict of interest

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