ORIGINAL ARTICLE

Heart Transplantation in Chagas Cardiomyopathy: 23-Year Follow-Up in a Referral Center

Trasplante cardíaco en miocardiopatía chagásica: 23 años de experiencia en un centro de referencia

ROSARIO DELLA CELLA FIGUEREDO[1], MARÍA F. RENEDO[1, MTSAC], DANIEL O. ABSI[1,4], ELIÁN F. GIORDANINO[1, MTSAC], ALDANA S. AMERI[1], LILIANA E. FAVALORO[1], ELIZABETH MADSEN[2], CARLOS A. VIGLIANO[3], ROBERTO R. FAVALORO[1,4, MTSAC], ALEJANDRO M. BERTOLOTTI[1,4]

ABSTRACT

Background: Chagas disease affects about 6 million people in Latin America, and 25 to 35% progress to Chagas cardiomyopathy (ChCM). Heart transplantation (HTx) is a therapeutic option in advanced stages.
Objectives: The aim of this study is to compare survival of patients with HTx due to ChCM versus those transplanted for other etiologies and to analyze the incidence of Chagas disease reactivation (Ra) and its impact on survival in this group of patients.
Methods: Patients undergoing HTx between August 1998 and March 2021 were retrospectively evaluated. Survival was analyzed using Kaplan-Meier curves and the log-rank test. The diagnosis of Ra was performed by molecular methods, Strout's test in peripheral blood, myocardial tissue or skin tissue.
Results: Of 606 patients with Htx, 39(6.4%) presented ChCM. Mean follow-up was 4.4 years (interquartile range 1.2-8.6). Mean age of the subgroup with ChCM was 51 years (IQR 45-60) and 28 were men (72%). Reactivation was documented in 38.5% of the patients. Survival at 1, 5 and 10 years in HTx recipients due to ChCM and Ra versus no Ra was 85%, 76% and 61% versus 72%, 55% and 44%, respectively (p = 0.3). Survival at 1, 5 and 10 years in HTx recipients due to ChCM versus HTx for other causes was 79%, 65% and 50% versus 79%, 62% and 47%, respectively (p = 0.5).
Conclusion: In our series we did not find statistically significant differences in survival of heart transplant recipients due to ChCM versus those transplanted due to other reasons. Survival in patients with Chagas disease reactivation and those without reactivation was also similar.

Key Words: Chagas Cardiomyopathy - Heart Transplantation - Reactivation – Survival

RESUMEN

Introducción: La enfermedad de Chagas afecta aproximadamente a 6 millones de personas en América Latina. El 25 a 35% evoluciona hacia la Miocardiopatía Chagásica (MCh). Una opción terapéutica en sus estadios avanzados es el trasplante cardíaco (TxC).
Objetivos: Comparar la supervivencia de pacientes con TxC por MCh frente a otras etiologías. Analizar la incidencia de la reactivación (Ra) de enfermedad de Chagas y su impacto en la supervivencia en este subgrupo de pacientes.
Material y métodos: Se evaluaron retrospectivamente pacientes con TxC entre agosto 1998 y marzo 2021. Se analizó la su¬pervivencia mediante curvas de Kaplan-Meier y log rank test. El diagnóstico de Ra se realizó mediante métodos moleculares, prueba de Strout en sangre periférica, tejido miocárdico y/o cutáneo.
Resultados: De 606 pacientes con TxC, 39 (6,4%) presentaban MCh. Seguimiento medio 4,4 años (Rango Intercuartilo 1,2-8,6). Edad subgrupo MCh 51 años (RIC 45-60). Hombres 28 (72%). Se documentó Ra en el 38,5% de los pacientes. Supervivencia a 1, 5 y 10 años en TxC por MCh con Ra versus no Ra: 85%, 76% y 61% versus 72%, 55% y 44% (p = 0,3). Supervivencia a 1, 5 y 10 años en TxC por MCh versus TxC por otras causas: 79%, 65% y 50% versus 79%, 62% y 47% (p = 0,5).
Conclusión: En nuestra serie no se encontró diferencia estadísticamente significativa en la supervivencia de los pacientes trasplantados cardíacos por MCh en comparación con aquellos trasplantados por otras causas; así como tampoco entre los pacientes que reactivaron la enfermedad de Chagas y los que no lo hicieron.

Palabras clave: Miocardiopatía Chagásica - Trasplante Cardíaco - Reactivación - Supervivencia

Rev Argent Cardiol 2022;90:46-53. http://dx.doi.org/10.7775/rac.v90.i1.20472

Received: 10/21/2021 – *Accepted:* 01/03/2022

Address for reprints: Rosario della Cella Figueredo - Av Belgrano 1782 - 1093- CABA – E-mail; rochidcf@gmail.com ; rfiguere@ffavaloro.org

This work received the 2021 Argentine Congress of Cardiology Award

[1] Heart Failure, Mechanical Circulatory Support and Cardiac Transplantation, Department of Intrathoracic Transplantation,
[2] Department of Epidemiology and Infectious Diseases,
[3] Department of Anatomical Pathology, Institute for Translational Medicine, Transplantation and Bioengineering (*CONICET-Universidad Favaloro*),
[4] Department of Cardiovascular Surgery. *Hospital Universitario Fundación Favaloro*. Buenos Aires, Argentina

INTRODUCTION

Chagas disease, caused by the protozoan Trypanosoma cruzi (T. cruzi) is a Latin American endemic disease that has spread worldwide due to migration of infected people in the last decades and affects approximately 6 million people in the region. According to recent estimations of the Pan American Health Organization (PAHO), Chagas disease shows an annual incidence of 30 000 new cases with 12 000 deaths per year and is considered a major health care problem strongly associated with social, economic and cultural deficits. (1)

Longitudinal studies reveal that 25-35% of those infected progress to the chronic phase of the disease, characterized mainly by gastrointestinal and cardiac involvement, which is the most common clinical manifestation and has the greatest impact on morbidity and mortality. (2) Chagas cardiomyopathy (ChCM) is characterized by chronic myocarditis, fibrosis, microvascular damage and cardiac remodeling which produce conduction system abnormalities, thromboembolism, apical or posterobasal left ventricular aneurysms and progression to dilated cardiomyopathy in 10% of the cases. (3,4) Some years ago, ChCM was considered a potential contraindication for heart transplantation (HTx) due to the high incidence of disease reactivation (Ra) associated with immunosuppressive therapy and treatment of acute graft rejection. Nowadays, HTx is an effective and safe therapeutic option in patients with advanced heart failure. (5,6)

The diagnosis of Chagas disease Ra is made by detecting the parasite in blood or tissues. A monitoring strategy using specific diagnostic methods to anticipate the onset of symptoms is essential, since if Ra is treated early and appropriately, it rarely has a torpid course. The episodes of Chagas disease Ra may be asymptomatic or have different clinical presentations: unspecific symptoms, skin involvement, myocarditis and, less commonly, central nervous system involvement. (7,8)

The main aim of this study is to compare the survival of patients who underwent cardiac transplantation for ChCM versus those transplanted for other causes, and to analyze the impact on short- and mid-term survival in those patients with Chagas disease reactivation in a high-complexity center in Latin America.

METHODS

Population and definition of variables

We retrospectively evaluated patients who underwent HTx in Hospital Universitario Fundación Favaloro between August 1998 and March 2021 and evaluated the survival of patients with HTx due to ChCM versus those transplanted for other reasons.

All the patients underwent clinical follow-up and surveillance biopsies according to the institutional protocol. The diagnosis of Ra was performed by polymerase chain reaction (PCR) to amplify sequences of kDNA minicircles (kDNA-PCR) and spliced-leader genes (SL-DNA-PCR, (9,10) Strout's test in peripheral blood, or by myocardial tissue or skin tissue. The treatment used in the cases of Ra was benznidazole 5 mg/kg/day for 60 days. Nifurtimox was used as alternative therapy in case of intolerance. Immunosuppressive therapy was initiated in the immediate postoperative period with corticosteroids, calcineurin inhibitors (tacrolimus or cyclosporin) and antiproliferative agents (azathioprine in Chagas disease HTx and mycophenolate in non-Chagas disease HTx).

The diagnosis of graft rejection was made based on clinical and echocardiographic suspicion and was confirmed by endomyocardial biopsy (EMB), considering positive reactivation in case of grade ≥2R (ISHLT 2004 classification) or ≥ 3A (ISHLT 1990 classification) for cellular rejection, and pAMR ≥1 for immunopathologic or histopathologic antibody-mediated rejection (ISHLT 2011 classification). (11,12)

In isolated cellular rejection treatment consisted of methylprednisolone and was associated with plasmapheresis, polyclonal antibodies and immunologlobulin in antibody-mediated or mixed rejections. The presence of graft vascular disease (GVD) was evaluated with coronary angiography and intravascular ultrasound. (13)

Statistical analysis

Continuous variables with parametric and non-parametric distribution were expressed as mean ± standard deviation, or median and interquartile range (IQR 25%-75%), respectively. Categorical variables were expressed as percentages and absolute values. The Student's t test or the Mann Whitney test were used to compare continuous variables according to their distribution and the Fisher's exact test was used to compare nominal variables. Survival at 1, 5 and 10 years was analyzed in a Mantel-Cox model; the corresponding curves were built using the Kaplan-Meier method and compared with the log-rank test. A p value < 0.05 was considered statistically significant.

RESULTS

Baseline characteristics of the population

A total of 606 HTx recipients were included from August 1998 to March 2021. The most common etiologies were non-ischemic (41%) and ischemic (31%) cardiomyopathies. The HTx program for patients with Chagas disease started in our center 23 years ago. Since then, 39 (6.4%) HTx have been performed in patients with end-stage ChCM (Figure 1). Median follow-up of the population was 4.4 years (IQR 1.2-8.6).

The baseline characteristics of the patients with Chagas CM undergoing HTx are displayed in Table 1. Median age was 52 years (IQR 41-59) and 28 (72%) were men. Venoarterial extracorporeal membrane oxygenation (VA-ECMO) was used in 17 patients, 1 patient required intra-aortic balloon pump and 1 patient required univentricular support with Berlin Heart EXCOR ventricular assist device. Nineteen (48.7%) patients underwent emergency transplants, 14 (35.9%) underwent urgent transplants and 6 (15.4%) transplants were elective. Only one patient underwent combined heart and kidney transplantation. Thymoglobulin was used as induction agent in 6 patients (15.4%). The initial immunosuppression was based on corticosteroids, cyclosporine and azathioprine. In a second stage, it was modified to a de novo scheme with corticosteroids, tacrolimus and azathioprine. During follow-up, corticosteroid doses were progressively reduced in the first 6 months fol-

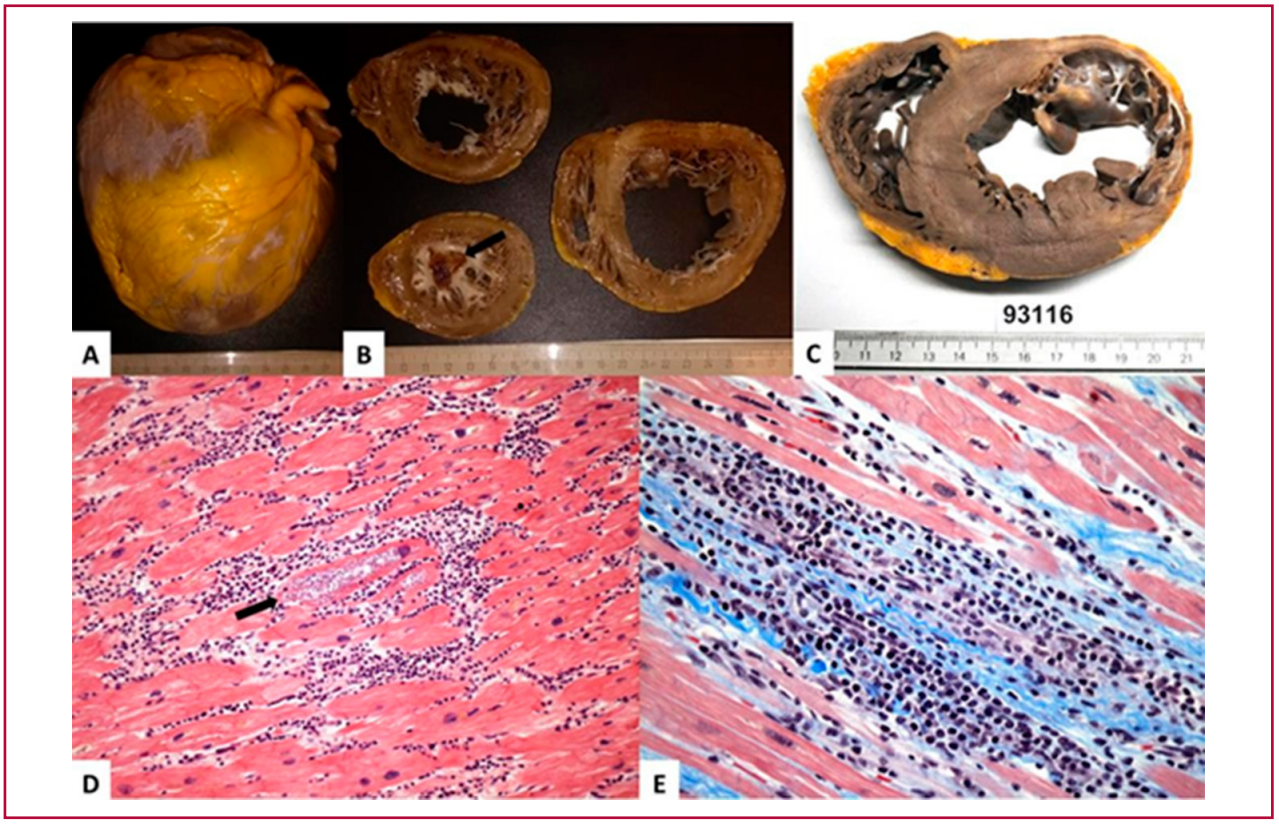

Fig. 1. Explants with chronic dilated Chagas cardiomyopathy. **A.** Macroscopic appearance of the native heart of a patient transplanted for chronic dilated Chagas cardiomyopathy. The pericardium has whitish areas slightly elevated at the level of the right anterior aspect, following the branches of the anterior descending coronary artery and in the ventricular apex. **B.** Serial sections along the short axis of the same case. The cardiac chambers are dilated, the endocardium is thickened and has a whitish appearance and a thrombus attached at the level of the ventricular apex (arrow). **C.** Macroscopic appearance of the native heart of a patient transplanted for chronic dilated Chagas cardiomyopathy. A ventricular aneurysm is observed at the level of the left ventricular posterolateral wall. **D.** Histological appearance of a section of the interventricular septum from a native heart. The cardiomyocytes with amastigotes nests (arrow) are surrounded by heavy inflammatory infiltrate with predominance of mononuclear cells. (Section stained with haematoxylin and eosin x200). **E.** Histologic appearance of an area with heavy myocarditis, with cardiomyocyte damage and replacement fibrosis. (Masson's trichrome staining x400).

lowing transplantation and were finally discontinued. In those patients with > 2 episodes of rejection, azathioprine was replaced by mycophenolate. In case of renal failure or GVD, treatment with m-TOR inhibitors (rapamycin or everolimus) was indicated. Eleven patients (28.2%) presented ≥ 2 episodes of cellular rejection > 2R. Two patients presented antibody-mediated rejection (pAMR ≥1). Neoplasms occurred in 15.4% of the patients and included skin cancer (2 patients), post-transplant lymphoproliferative disease (3 patients) and renal carcinoma (1 patient). Five years after transplantation, 23.1% of the patients developed GVD (Table 2). The main causes of death were sepsis and graft rejection.

Reactivation

Chagas disease Ra was documented in 15 patients (38.5%): 5 presented parasitemia, 7 had skin involvement (Figure 2 A-E) and 1 patient presented combined reactivation with skin involvement and myocarditis (Figure 2 F-J). In 53.3% Ra occurred within 90 days after HTx and in 73.3% after rejection treatment. All the episodes were successfully treated with benznidazole.

Survival

There were no statistically significant differences in survival of patients who underwent HTx due to ChCM vs. HTx due to other causes at 1, 5 and 10 years (79%, 65% and 50% versus 79%, 62% and 47% respectively; p = 0.5) (Figure 3A). Survival at 1, 5 and 10 years in patients with HTx due to Chagas CM and Ra was 85%, 76% and 61% versus 72%, 55% and 44% in those without Ra (p = 0.3). (Figure 3B).

DISCUSSION

In our series, the incidence of Ra was similar to the one reported in the literature. The high incidence of Ra of T. cruzi infection in patients with HTx varies between 23% and 75% (7) and has been linked to treatment of acute graft rejection and to the use of mycophenolate mofetil as immunosuppressive agent.

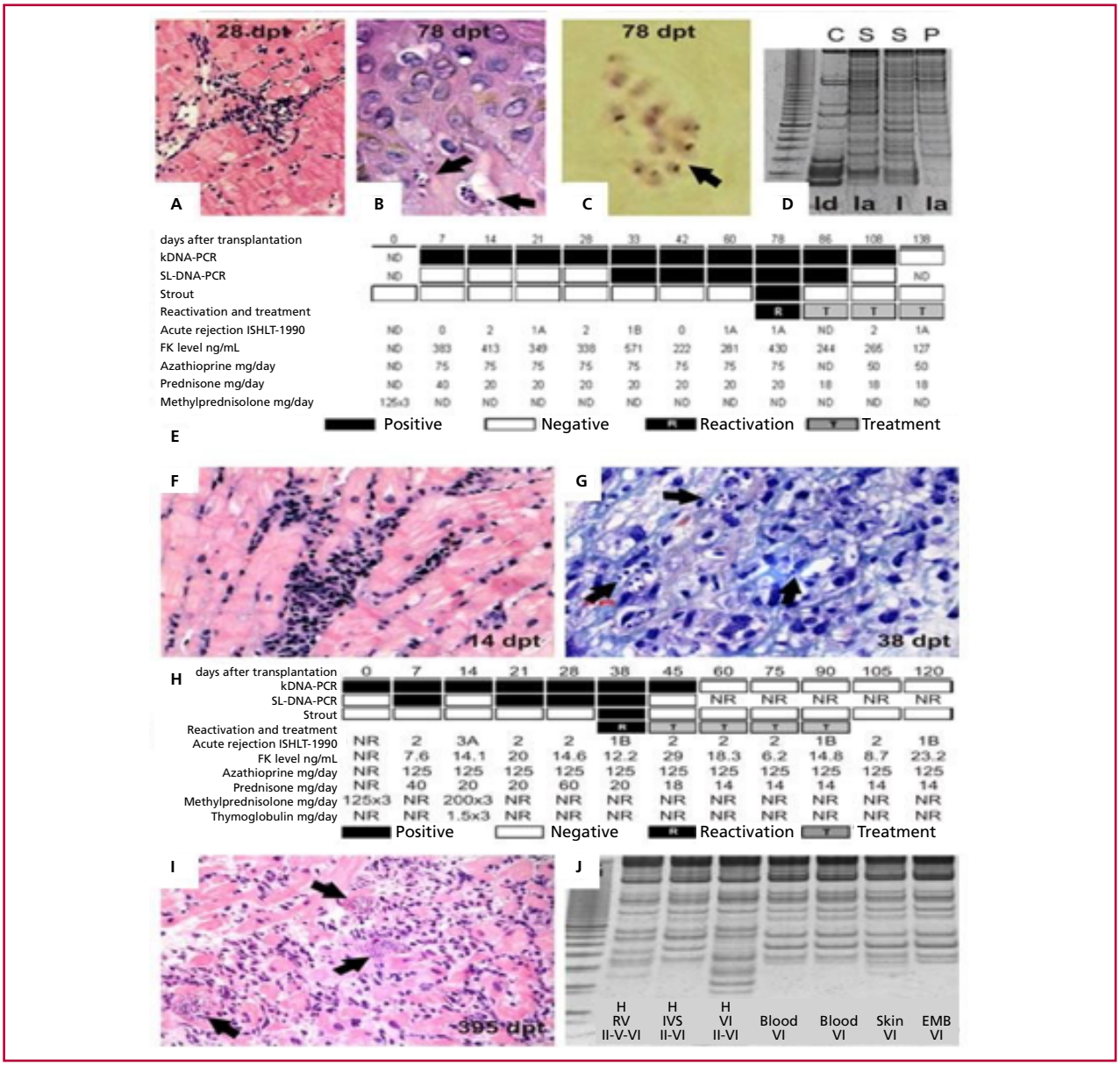

Fig. 2. Chagas disease reactivation after transplant. **A.** Surveillance endomyocardial biopsy (day 28 after transplant) with mild lymphocytic infiltration and focal cardiomyocytes damage (mild cellular rejection). **B.** Skin biopsy on day 78 after transplant. Amastigotes nests are observed on the dermoepidermal junction (arrows) (Section stained with haematoxylin and eosin x400). **C.** Magnification of an amastigotes nest. (Gallego's trichrome staining x1000). **D.** Restriction fragment length polymorphism obtained from kDNA-PCR amplicons analyzed by electrophoresis. Discrete typing units (DTUs) obtained from native heart (C), peripheral blood (S) and skin (P) (site of reactivation) correspond to T. cruzi type 1. **E.** Patient's follow-up after heart transplantation. kDNA-PCR = polymerase chain reaction amplification of T. cruzi kinetoplast minicircle DNA (limit of detection in blood = 1 parasite/10 mL); SL-DNA-PCR = PCR with spliced-leader genes (limit of detection in blood = 200 parasites/10 mL). FK = Tacrolimus. NR = Not performed. An episode of reactivation treated with benznidazole is shown with the incidence of rejection, tracrolimus levels and doses of immunosupressive agents. **F.** Endomyocardial biopsy of the interventricular septum performed in another patient on day 14 after transplant. Multifocal monocyte infiltrate and cardiomyocyte damage are observed (cellular rejection grade 3A of the ISHLT-1990 classification) (Section stained with haematoxylin and eosin x400). **G.** Skin biopsy on day 38 after transplant. Subcutaneous tissue with amastigotes nests (arrow) and heavy inflammatory infiltrate with predominance of mononuclear cells and neutrophils (Giemsa stain x1000). **H.** Patient follow-up after heart transplant. **I.** Surveillance endomyocardial biopsy performed on day 395 after transplant. Acute Chagas myocarditis (reactivation). Cardiomyocytes with amastigotes nests, edema and heavy inflammatory infiltrate with mononuclear cells and neutrophils (Section stained with haematoxylin and eosin x400). **J.** Restriction fragment length polymorphism (RFLP) obtained from kDNA-PCR amplicons analyzed by gel electrophoresis and Sybr Green dye staining in the explanted heart, in blood and in reactivation sites during follow-up after transplant. H = explanted heart. RV = right ventricle. IVS = interventricular septum. LV = left ventricle. EMB = endomyocardial byopsy. On bottom, T. cruzi DTUs demonstrated by the analysis of blood and tissues. This case corresponded to T. cruzi monoclonal strain Tc VI

Table 1. Baseline characteristics of the patients with Chagas cardiomyopathy

Variable	Total population (n = 39)
Recipient's characteristics	
Age (years), median and IQR	51 (45-60)
Male gender, n (%)	28 (71.8%)
BMI (kg/m2), median and IQR	23.3 (20-26.2)
Comorbidities, n (%)	
Diabetes, n (%)	3 (7.7%)
Smoking habits, n (%)	12 (30.8%)
Heart transplant waiting list, n (%)	
Elective, n (%)	6 (15.4%)
Urgent, n (%)	14 (35.9%)
Emergency, n (%)	19 (48.7%)
Donor's characteristics	
Male gender, n (%)	33 (84.6%)
Age (years)	22 (17.7-27)

BMI: Body mass index. IQR: Interquartile range

Table 2. Follow-up after transplant in Chagas cardiomyopathy

Variable	Population (n = 39)
Immunologic complications. n (%)	
≥ 2 cellular rejection > 2R	11 (28.2%)
Antibody-mediated rejection	2 (5.1%)
GVD	9 (23.1%)
Neoplasms [n (%)]	6 (15.4%)
Skin cancer	2 (33.3%)
Post-transplant lymphoproliferative disease	3 (50%)
Renal carcinoma	1 (16.7%)
Reactivation, n (%)	15 (38.5%)
90 days after transplant	8 (53.3%)
After rejection treatment	11 (73.3%)
Type of reactivation, n (%)	
Parasitemia	5 (33.3%)
Skin	7 (46.7%)
Myocarditis	2 (13.3%)
Combined	1 (6.7%)

GVD: graft vascular disease

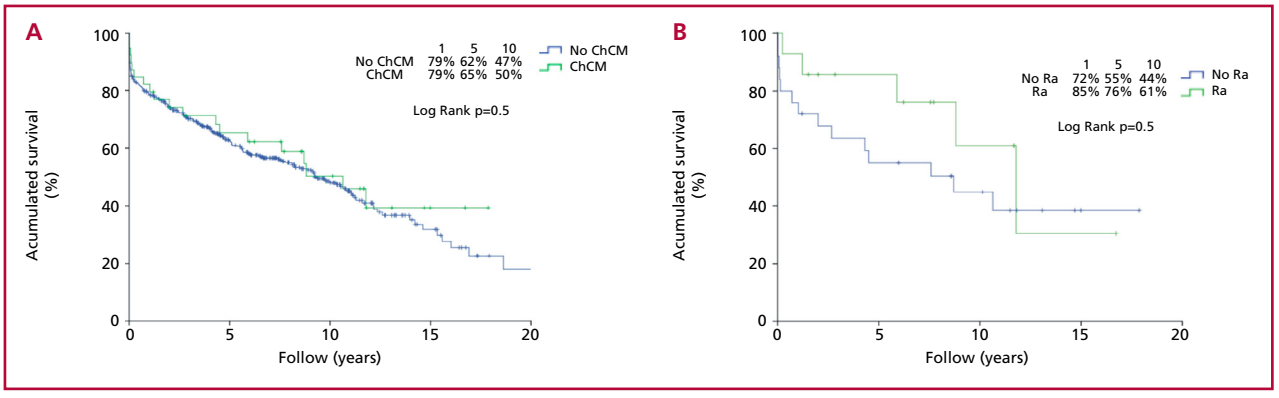

Fig. 3. A. Survival at 1, 5 and 10 years in heart transplant recipients due to Chagas cardiomyopathy (ChCM) versus the general population. **B.** Survival at 1, 5 and 10 years in heart transplant recipients due to Chagas cardiomyopathy with reactivation (Ra) versus those without reactivation.

(5,14) Although this drug has been reported to increase the incidence of Chagas disease Ra compared with azathioprine, the evidence is not strong enough to define the ideal immunosuppression regimen for ChCM transplant recipients. (15,16) In the population analyzed, maintenance of immunosuppressive treatment was based on a triple scheme including corticosteroids, calcineurin inhibitors (cyclosporine or tacrolimus) and antiproliferative agents (azathioprine or mycophenolate mofetil). In those patients with > 2 episodes of rejection, azathioprine was replaced by mycophenolate; mTOR inhibitors were preferred over calcineurin inhibitors in patients with progressive renal failure or GVD.

Patients with Chagas disease require close monitoring for the early detection of Ra episodes. There are two circumstances in which the risk of disease Ra is higher: the first months after transplantation and after treatment of an episode of rejection, situations in which the immunosuppressive regimen is intensified.

The episodes of Ra may be asymptomatic or present as subcutaneous involvement (nodules or paniculitis), myocarditis and, less commonly, central nervous system involvement (meningoencephalitis or brain abscess). Although the clinical diagnosis of Ra requires the presence of a consistent clinical picture and parasitological evidence, the differential diagnosis between graft rejection and Ra is a challenge and can sometimes hinder the early initiation of appropriate treatment. (15) This is attributed to two main factors: the inflammatory infiltrates present in EMB are similar to those found in the setting of rejection and the amastigotes nests of T. cruzi characteristic of myocarditis are a rare histopathological finding. Although the gold standard for documenting Ra is the microscopic observation of the parasite in blood

by Strout's method (thick drop), this method has low sensitivity due to the low levels of parasitemia at the onset of the Ra events. On the other hand, serological tests are not useful because the results are positive in the chronic phase of the disease. In recent decades, the development of molecular methods has become important. (9,10,17) The detection of DNA by PCR techniques has allowed early diagnosis, anticipating the symptomatic phase of Chagas reactivation and the microscopic presence of trypomastigotes, and is also useful for follow-up and to monitor the response to treatment. (5,16,17)

To date, there are no universally validated screening and monitoring protocols for the follow-up of patients with HTx due to Chagas CM because of the lack of robust and conclusive evidence. For this reason, their implementation depends on the protocols of each institution, and will also be based on the availability of technical and human resources and the socioeconomic context of the patients. An approach to consolidate decisions in these complex clinical scenarios is the development of algorithms reached by consensus and internally validated by the treating multidisciplinary team made up of specialists in advanced heart failure, infectious disease specialists and pathologists.

In our study, we observed that the survival rate in heart transplant recipients with Chagas disease and without Chagas disease was similar and consistent with the observation reported by Bestetti et al. in a systematic review in Brazil. (7,15)

The retrospective nature of this single-center study in one limitation of this investigation conducted on a reduced sub-population of patients with ChCM which could not be sufficient to demonstrate statistically significant differences. Nevertheless, the follow-up period was long. Further prospective and multicenter analyses with a larger sample of patients will help determine the most appropriate immunosuppressive regimen for these patients and thus develop universal protocols for close monitoring during follow-up.

CONCLUSIONS

Our institutional experience across the decades still supports that heart transplantation is a safe and effective treatment for patients with Chagas cardiomyopathy, as survival of these patient is similar to that of those transplanted for other causes. Although reactivation of Trypanosoma cruzi infection is a common complication, a timely implementation of the currently available therapies has shown a favorable outcome in the follow-up of these patients, with no impact on their prognosis.

Conflicts of interest

None declared.

(See authors' conflict of interests forms on the web/Additional material.)

REFERENCES

1. https://www.paho.org/es/temas/enfermedad-chagas. Accedido 06 septiembre 2021.

2. Rassi A Jr., Rassi A, Marin-Neto JA. Chagas disease. Lancet 2010;375:1388–402. 10.1016/S0140-6736(10)60061-X.

3. Chao C, Leone JL, Vigliano CA. Chagas disease: Historic perspective. Biochim Biophys Acta Mol Basis Dis 2020;1866:165689. https://doi.org/10.1016/j.bbadis.2020.165689.

4. Benassi MD, Avayú DH, Tomasella MP, Valera ED, Pesce R, Lynch S, y cols. Consenso Enfermedad de Chagas 2019. Rev Argent Cardiol 2020;88(Suplemento 8):1-74.

5. Diez M, Favaloro L, Bertolotti A, Burgos JM, Vigliano C, Lastra MP, et al. Usefulness of PCR strategies for early diagnosis of Chagas' disease reactivation and treatment follow- up in heart transplantation. Am J Transplant 2007;7:1633–40. https://doi.org/10.1111/j.1600-6143.2007.01820.x.

6. Favaloro L, Peradejordi Lastra M, Nagel C. Enfermedad de Chagas y Trasplante de órganos. En: Viotti R, Vigliano C (editores). Enfermedad de Chagas. Un enfoque práctico basado en la investigación médica. Buenos Aires: Panamericana; 2015. p. 303-20.

7. Bestetti RB, Theodoropoulos TA. A systematic review of studies on heart transplantation for patients with end-stage Chagas' heart disease. J Card Fail 2009;15:249-55. https://doi.org/10.1016/j.cardfail.2008.10.023

8. Vieira JL, Távora FRF, Sobral MGV, Vasconcelos GG, Almeida GPL, Fernandes JR, , et al. Chagas Cardiomyopathy in Latin America review. Curr Cardiol Rep 2019;21:8. 10.1007/s11886-019-1095-y.

9. Schijman AG, Vigliano C, Burgos J, Favaloro R, Perrone S, Laguens R, et al: Early diagnosis of recurrence of Trypanosoma cruzi infection by polymerase chain reaction after heart transplantation of a chronic Chagas' heart disease patient. J Heart Lung Transplant 2000;19:1114-7. https://doi.org/10.1016/s1053-2498(00)00168-6.

10. Burgos JM, Diez M, Vigliano C, Bisio M, Risso M, Duffy T, et al. Molecular identification of Trypanosoma cruzi discrete typing units in end-stage chronic Chagas heart disease and reactivation after heart transplantation. Clin Infect Dis 2010;51:485-95. https://doi.org/10.1016/s1053-2498(00)00168-6.

11. Stewart S, Winters GL, Fishbein MC, Tazelaar HD, Kobashigawa J, Abrams J, et al. Revision of the 1990 working formulation for the standardization of nomenclature in the diagnosis of heart rejection. J Heart Lung Transplant 2005;24:1710–20. https://doi.org/10.1016/j.healun.2005.03.019

12. Berry GJ, Burke MM, Andersen C, Bruneval P, Fedrigo M, Fishbein MC, et al. The 2013 International Society for Heart and Lung Transplantation Working Formulation for the standardization of nomenclature in the pathologic diagnosis of antibody-mediated rejection in heart transplantation. J Heart Lung Transplant 2013;32:1147-62. https://doi.org/10.1016/j.healun.2013.08.011

13. Mehra MR, Crespo-Leiro MG, Dipchand A, Ensminger SM, Hiemann NE, Kobashigawa JA, et al. International Society for Heart and Lung Transplantation working formulation of a standardized nomenclature for cardiac allograft vasculopathy. J Heart Lung Transplant 2010;29:717-27. https://doi.org/10.1016/j.healun.2010.05.017

14. Bacal F, Silva CP, Bocchi EA, Pires PV, Moreira LF, Issa VS, et al. Mychophenolate mofetil increased Chagas disease reactivation in heart transplanted patients: Comparison between two different protocols. Am J Transplant 2005;5:2017-21. https://doi.org/10.1111/j.1600-6143.2005.00975.x

15. Bocchi EA, Fiorelli A. The paradox of survival results after heart transplantation for cardiomyopathy caused by Trypanosoma cruzi. First Guidelines Group for Heart Transplantation of the Brazilian Society of Cardiology. Ann Thorac Surg 2001;71:1833-8. https://doi.org/10.1016/S0003-4975(01)02587-5

16. Benatti RD, Oliveira GH, Bacal F. Heart transplantation for Chagas cardiomyopathy. J Heart Lung Transplant 2017;36:597–603. https://doi.org/10.1016/j.healun.2017.02.006

17. Da Costa PA, Segatto M, Durso DF, Carvalho Moreira WJ, Junqueira LL, de Castilho FM, et al. Early polymerase chain reaction detection of Chagas disease reactivation in heart transplant patients. J Heart Lung Transplant 2017;36:797-805. https://doi.org/10.1016/j.healun.2017.02.018