

**EXPERTS' REVIEW (Original language)**

# Cardiac transplantation for Chagas' disease

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Over the last 20 years the immunosuppression protocols in chagasic heart transplanted patients lived at least three different moments and we testified several changes and discoveries on Chagas' disease reactivation, mortality and neoplasias development. The primary phase was important especially because, until that time, Chagas' disease was an absolute contra-indication for transplantation.

The second phase started when immunosuppression protocol adjustment was made, with lower dosage to avoid adverse effects, especially neoplasias.

Nowadays strategies to change the immunosuppression, especially replacement of mycophenolate mofetil by azathioprine were shown to be effective in reducing Chagas' disease reactivation.

Cardiac transplantation for Chagas' disease is a reality. Although chagasics have several different implications when submitted to the transplant comparing to others aetiologies, actually these difficulties are well known, so treatments and preventive strategies are also better established.

**Keywords:** Chagas' disease - Cardiac transplantation - Immunosuppression - Reactivation

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## Introduction

Chagas' disease is a trypanosomiasis caused by a protozoan named *Trypanosoma cruzi*, which is endemic in Latin America from Mexico to Southern Argentina and Chile<sup>1</sup>. It is classically transmitted by contact with triatomine's feces. Blood derivatives and vertical transmission also can occur. The chronic form of the disease frequently compromises the digestive system and heart. The cardiac form is the most aggressive, attacking about 30% of infected patients<sup>2</sup>. This disease is responsible for up to 18% of the cases of refractory heart failure in Brazil<sup>3</sup>. The clinical manifestations of cardiac damage are variable. In the most benign cases there are alterations of cardiac rhythm with small changes in diastolic function, up to serious atrioventricular block, complex ventricular arrhythmias, sudden death and diffuse damage of ventricular contraction by chronic myocardial aggression,

characterized as chagasic cardiomyopathy<sup>4</sup>.

Chagas' cardiomyopathy is considered the worst aetiology for heart failure when compared to others. It has been suggested that a more intense inflammatory activation, arrhythmias, and a high incidence of embolic events could be the responsables for the excessive mortality. Mocelin et al. showed that inflammatory activation in Chagas' heart disease differs from idiopathic dilated cardiomyopathy and is associated with heart failure severity<sup>5</sup>.

Reactivation of the *Trypanosoma cruzi* infection after transplantation persists a real problem in the clinical follow-up, however an acceptable survival was demonstrated in many studies conducted on different organs and tissues<sup>6-10</sup>. With those results Chagas' disease is no longer a contraindication for transplantation, and the criteria for patient selection for transplantation among Chagas' disease patients are similar to those used for nonchagasics, except for chagasic megaesophagus or megacolon, which can be considered contraindications<sup>11</sup>.

## Chagas' disease diagnosis

The diagnostic criteria for chronic Chagas' disease were a combination of epidemiological data, positive serological tests for anti-*T cruzi* antibodies (complement fixation and indirect immunofluorescence) and a compatible clinical syndrome (in heart disease it is also important to exclude other cause for the cardiomyopathy). Complement-fixation tests (Machado-Guerrero) are considered positive when the reaction is observed in a serum dilution equal to or greater than 1:8 and the indirect

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immunofluorescence equal to or greater than 1:32 in at least two different assays.

### Immunosuppression in chagasic heart transplanted patients

Over the last 20 years the immunosuppression protocols in chagasic heart transplanted patients lived at least three different moments. During this period we testified several changes and discoveries about Chagas' disease reactivation, mortality and neoplasias. We will analyze the treatment of chagasic patients, divided in three different periods (Phases 1, 2 and 3).

#### Phase 1

That was an important phase especially because until that time Chagas' disease was an absolute contra-indication for transplantation. During that first period we accumulated experience and several good results which proved the viability of this surgery for this aethiology. Bocchi et al. published a review where they showed that, compared to different aethiologies, chagasics had the best survival rate after cardiac transplant<sup>12</sup> (Figure 1). The survival probability of patients submitted to heart transplantation for chagasic aethiology at 1, 6 months, 1, 2, 4, 6, 8, 10, and 12 years was 83%, 76%, 71%, 62%, 57%, 55%, 55%, 46%, and 46%. The survival rate of patients who underwent transplants for the treatment of Chagas' heart disease was better in comparison with the total group survival ( $p:0.03$ ). Survival of chagasics was significantly better in comparison with idiopathic and ischemic cardiomyopathy ( $p:0.027$ ). Survival of chagasics was better than patients with ischemic cardiomyopathy in both short- and long-term follow-up. Reactivation of the *T. cruzi* infection was a rare cause of death and neoplasia was more frequent in chagasics.

The main reason explaining the better long-term survival rate after heart transplantation for Chagas' heart disease could be the low incidence of graft coronary artery disease, the patients were younger than other aethiologies and consequently with less comorbidities. Possible factors associated with this low incidence of graft coronary artery disease should be better investigated. On the other hand the high incidence of malignant neoplasias was probably caused by multiple factors such as reactivation of *T. cruzi* infection, benznidazole treatment, and immunological disorders associated with *T. cruzi* infection<sup>9</sup>.

#### Phase 2

The main objective of this second phase was the immunosuppression protocol adjustment with lower dosage to avoid adverse effects, especially neoplasias.

When they compared these two phases, it was found a significant difference between the number of Chagas' reactivation (2.3 per patient in the first group and 0.25 in the second group) and survival, which had better results in the group with low immunosuppression dosage ( $p<0.05$ ). There was no difference about number of rejection episodes between these two protocols. Malignant diseases developed during follow-up in 6 patients, 5 belonging to the earliest group (three lymphomas, two Kaposi's sarcoma and one squamous carcinoma).

These findings allowed to conclude that the reduction of cyclosporine dose was associated to a lower rate of Chagas' disease

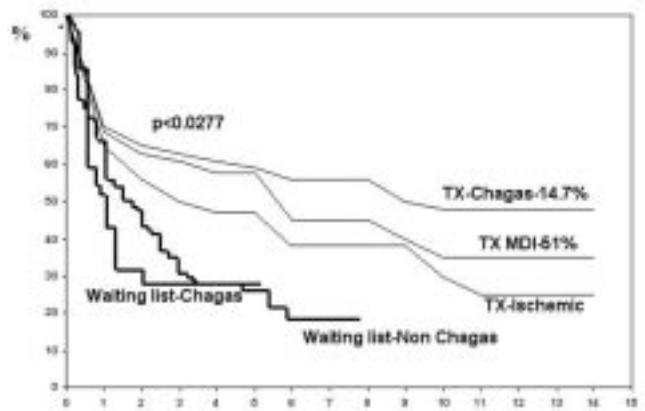


Figure 1. Comparison of survival of chagasic and non-chagasic patients submitted to cardiac transplantation. Adapted from Bocchi et al. Ann Thorac Surg 2001;71:1833-8.

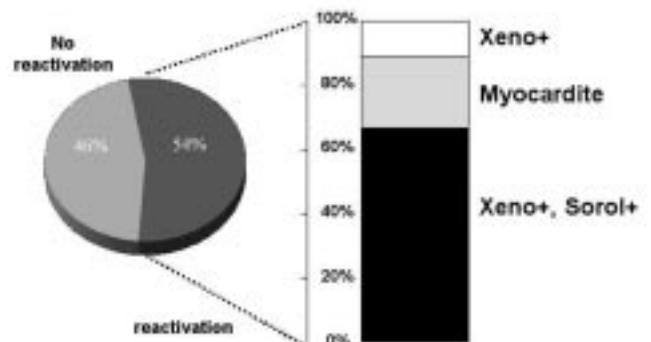


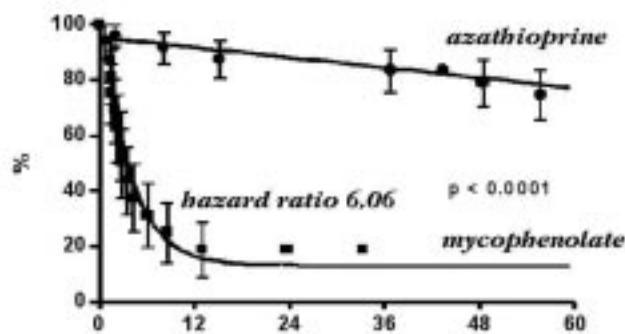
Figure 2. Chagas disease reactivation rate in a sub-group of patients with low doses of cyclosporine.

reactivation, neoplasias, and improved survival (Figure 2). Especially about neoplasias, it is important to remember that immunosuppressive agents have direct correlation with greater tumor incidence in this population. The neoplasias incidence is about four times greater among the immunosuppressed than the normal population. Cyclosporine has an inhibitory action on T cells, through interleukin-2, and alters elements controlling B-cells proliferation, resulting from viral infections or during the episodes of reactivation of latent virus. In this way, it predisposes to lymphoma appearance<sup>13</sup>.

#### Phase 3

As the Chagas' disease became a usual indication for transplantation, the *T. cruzi* reactivation monitoring turn necessary and was defined as a routine.

The *Trypanosoma cruzi* infection is specifically investigated at the time of routine endomyocardial biopsies and in the blood if there is clinical or laboratorial suspicious of Chagas' disease reactivation. In our experience, we routinely investigate reactivation in blood each 4 months (hemoculture, xenodiagnosis and QBC -quantitative buffy coat-). Recent articles have shown that polymerase chain reaction could be a sensitive and specific method for Chagas' reactivation diagnosis<sup>14,15</sup>. The diagnosis of Chagas' disease reactivation is considered when the parasite is detected in blood or tissues with inflammatory process surrounding it, in association with symptoms or signs attributable to infection



**Figure 3.** Free reactivation curve, comparing two different immunosuppression protocols. Adapted from Bacal et al. Am J Transplant 2005;5:2017-2021.

by *T. cruzi*. Chagasic myocarditis is diagnosed by the demonstration of the parasite surrounded by a myocardial inflammatory infiltrate according to the Dallas' criteria<sup>16</sup>. Parasitemia is diagnosed when *T. cruzi* is detected in blood samples. Episodes of parasitemia, myocarditis or Chagas' disease reactivation are already treated with benznidazole in a 5 mg/kg/day dosage for 60 days. Allopurinol at a daily dose of 600-900 mg is another option for the Chagas' disease reactivation<sup>17</sup> as Nifurtimox 8-10 mg/Kg<sup>2</sup>.

Since 2001 we included mycophenolate mofetil in our immunosuppression protocol as a replacement of azathioprine. After this change we noticed that the number of episodes of Chagas' disease reactivation increased. A retrospective analysis proved this clinical observation<sup>18</sup>. The use of mycophenolate mofetil did not change the number of rejections or survival curve when compared to the protocol with azathioprine, however increased the number of Chagas' disease reactivation ( $p < 0.0001$ , hazard ratio 6.06). These findings were determinant leading us to prescribe azathioprine again only for chagasic heart transplanted patients, in the place of mycophenolate mofetil. Another recent study from Bestetti et al. also revealed a high incidence of Chagas' reactivation with mycophenolate mofetil based immunosuppression<sup>19</sup> (Figure 3).

## Conclusion

Nowadays cardiac transplantation for Chagas' disease is a reality. Although chagasics have several different implications when submitted to the transplant comparing to others aetiologies, actually these difficulties are well known, so treatments and preventive strategies are also better established. The most important care is with the immunosuppressive dosages, which must be different and lower than used to others aetiologies.

## Resumo

### Transplante cardíaco para a doença de Chagas

Durante os últimos 20 anos o protocolo de imunossupressão em pacientes submetidos a transplante cardíaco por doença de Chagas vêm apresentando grandes mudanças, e testemunhamos descobertas na reativação da doença após transplante, na mortalidade e desenvolvimento de neoplasias. A primeira fase foi importante porque até aquele

momento a doença de Chagas era uma contra-indicação absoluta para transplante.

A segunda fase começou quando ajustes no protocolo de imunossupressão foram feitos, especialmente com doses inferiores de ciclosporina, evitando efeitos adversos, principalmente neoplasias.

Hoje em dia, estratégias para mudar a imunossupressão, com a substituição do micofenolato mofetil pela azatioprina mostrou-se efetiva na redução da reativação de doença de Chagas.

O transplante cardíaco para a doença de Chagas é uma realidade. Embora o transplante nesta etiologia apresente peculiaridades próprias, estas dificuldades hoje são bem conhecidas, propiciando melhores tratamentos e estratégias preventivas.

**Palavras chave:** Doença de Chagas - Transplante cardíaco - Imunossupressão - Reativação

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