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Liver Transplantation from Deceased Donors Serologically Positive for Chagas Disease

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The high mortality rates among patients waiting for liver transplantation has motivated the use of 'marginal livers', among which are included livers from *deceased* donors serologically positive for Chagas disease (CD). The present work describes the outcome of orthotopic liver transplantation in six patients with severe liver disease (Child Pugh C), with livers from donors serologically positive for CD. Transplantations were performed from November 2000 to January 2005, and the patients received prophylactic treatment with benznidazole for 60 days, as a recommended by the Brazilian Consensus in Chagas Disease. The transplantation procedures presented no technical problems, and all the patients were discharged from hospital. Five of them did not present side effects demanding interruption of the prophylactic treatment. Four of the patients were clinically well over 1 year after transplantation (mean follow-up of 42.1 months), with negative serological results for CD. Two patients died, one of them 6 months post surgery of sepsis due to biliary complication and other one due to pulmonary (tuberculosis) complications. They were both serologically negative for CD. These results suggest that liver transplantation from CD donors, followed by benznidazole prophylactic treatment, is an important therapeutic alternative for severe liver disease.

Key words: Deceased organs, liver transplantation, transplantation

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Introduction

In Sao Paulo, Brazil, the waiting time for orthotopic liver transplantation (OLT) in 2004 was in average 32 months (1). The resulting high mortality rate among patients in waiting lists, added to the occurrence of clinical complications demanding multiple hospitalizations and resulting in high medical–social costs, motivated the use of 'marginal livers' in our service (CETEFI—Hospital Beneficência Portuguesa de São Paulo). Livers from *deceased* donors serologically positive for Chagas disease (CD) were included in this category.

CD is a systemic infection caused by the parasite *Trypanosoma cruzi*, which affects mainly the heart and the digestive system (2). It is transmitted by contact with the vector (a triatomine insect) or by blood or blood derivatives transfusion, and is endemic in regions of Central and South America where around 16 or 18 million people are infected (3). The acute phase of CD is characterized by high parasite load. Affected individuals may be asymptomatic or present fever, skin manifestations (chagoma), hepatosplenomegaly and myocarditis. Clinical and parasite symptoms progressively decrease, due to therapy or to the host's immune response, and serologic tests are of fundamental importance for diagnosis (4).

The increasing shortness of organs for transplantation has stimulated the use of organs from donors with transmissible infectious diseases. Livers from donors with positive CD serology may be accepted when the death risk of the receptor during the waiting time is high (5). Other organs have also been transplanted from CD donors. The use of kidneys, for instance, has been suggested, followed by a careful postoperative control and treating patients with patent parasitemia or clinical signs of the disease (6). Souza et al. recently described nine cases of kidney transplantation from serologically positive donors to negative receptors. Immediately after surgery and during the next 14 days, all patients were treated with benznidazole (5 mg/kg/day), and none of them developed acute disease or presented seroconversion (7).

Successful cases of heart transplantation to patients with heart disease due to CD were performed in Brazil in 1996 (8). The patients received prophylactic treatment with benznidazole during the first 60 postoperative days, to avoid reactivation of CD.

The present work describes the outcome of OLT in six cases in which the donors were serologically positive for CD. The patients received prophylactic treatment with benznidazole for 60 days.

Table 1: Characteristics of patients transplanted with livers from donors serologically positive for CD

Age	Sex	Base disease	Child pugh	Immunosuppressive treatment	Prophylactic treatment	Serological test	Follow-up	Course
46	M	Hepatitis C	C	Cyclosporine, MMF and corticosteroids (blood level between 100 and 150 ng/mL for the the first 3 months)	Oral administration of 200 mg benznidazole every 12 hours for 60 days	Serum hemagglutination and enzyme immunoassay	17 months	Alive
54	M	Hepatitis C	C	Cyclosporine, MMF and corticosteroids (blood level between 100 and 150 ng/mL for the first 3 months)	Oral administration of 200 mg benznidazole every 12 hours for 60 days	TESE-blot assay)	59 months	Alive
39	M	Primary sclerosing cholanghitis	C	Tacrolimus, MMF and corticosteroids (blood level between 100 and 150 ng/mL for the first 3 months)	Oral administration of 200 mg benznidazole every 12 hours for 60 days	TESE-blot assay	23 months	Alive
47	F	Primary biliary cholanghitis	C	Tacrolimus, MMF and corticosteroids (blood level between 100 and 150 ng/mL for the first 3 months)	Oral administration of 200 mg benznidazole every 12 hours for 60 days	TESE-blot assay	79 months	Alive
42	M	Alcohol liver cirrhosis	C	Tacrolimus, MMF and corticosteroids (blood level between 100 and 150 ng/mL for the first 3 months)	Oral administration of 200 mg benznidazole every 12 hours for 60 days	Not tested	3 months	Died of sepsis, 103 days (arterial thrombosis)
47	M	Deficiency of alfa-1-trypsin	C	Tacrolimus, MMF and corticosteroids (blood level between 100 and 150 ng/mL for the first 3 months)	Oral administration of 200 mg benznidazole every 12 hours for 7 days	Not tested	4 months	Died of pulmonary tuberculosis

Materials and Methods

Liver transplantation, with preservation of the vena cava, was performed in six patients (five men and one woman), with mean age of 46 years, during the period between November 2000 and January 2005. Characteristics of the patients, treatment and other parameters are presented in Table 1.

The patients presented severe liver disease and were classified as Child Pugh C. Aetiology included liver cirrhosis due to HCV in two cases, whereas the remaining cases were due to primary biliary cirrhosis, alcohol liver cirrhosis, primary sclerosing cholanghitis and deficiency of alfa-1-trypsin.

Deceased donors were serologically positive for CD, as assessed by two different assays (ELISA and serum hemagglutination). All patients had negative serology for CD when transplantations were performed. Oral administration of 200 mg benznidazole every 12 h for 60 days was used for postoperative CD-specific prophylaxis, according to recommendation from Brazilian Health Authorities (4).

The postoperative follow up included the analysis of serum antibodies and parasitemia, 3 and 6 months after transplantation. The parasite was searched for in peripheral blood. The diagnosis of reactivation of CD was considered when the parasite was detected in blood or tissues surrounded by inflammation, in association with symptoms or signs attributable to infection by *T. cruzi*. One year after surgery, asymptomatic patients were analyzed by serum hemagglutination and enzyme immunoassay, or by the TESE-blot assay for anti-Tc antibodies (IgG and IgM).

The immunosuppressive treatment of patients with hepatitis C included administration of Cyclosporine, adjusted to a blood level between 100 and 150 ng/mL for the first 3 months posttransplant. The other patients were treated with Tacrolimus adjusted to a blood level of 7–10 ng/mL. Mycophenolate mofetil (MMF) and corticosteroids, in conventional doses, were also administered. Acute cell rejection, confirmed by liver biopsy, would be treated by corticoid pulse therapy in more severe cases, and by adjustment of inhibitory levels of calcineurin and MMF in other cases.

All patients signed informed consent for transplantation with a liver serologically positive for CD and for participation in the study. They were aware of the prophylactic treatment received and risk of transmission of the disease.

Results

Transplantation procedures presented no technical problems, and the patients were discharged from hospital. Five of them did not present any kind of complications that demand interruption of the benznidazole prophylactic treatment. The sixth patient presented persistent temperature over 37.5°C, severe anemia and pneumonia on the first week after transplantation, receiving intensive therapy. He also developed gastric paresis, possibly secondary to sepsis, so that the benznidazole treatment was interrupted from the eighth posoperative day on. The patient was discharged 2 months after transplantation, but 4 months later had another pneumonic episode with sepsis. Parasitemia analyses did not show evidence of CD. Thoracoscopy was indicated, and pleural biopsy allowed diagnosis of pulmonary tuberculosis. The patient died in a short period, despite receiving specific therapy.

A second patient presented complications, and was readmitted 2 months after transplantation with high level of cholestatic enzymes and fever. Cholangiography showed irregularity of the entire biliary tree, secondary to a thrombosis of the hepatic artery. Due to a general health deterioration secondary to cholangitis, there was no time for a liver retransplantation, since the Brazilian legislation gives priority to patients with arterial thrombosis diagnosed only on the first postoperative month. The patient died of sepsis 103 days after surgery, and analysis of parasitemia had negative results for CD.

No acute cellular rejection was observed in any of the patients, and four of the patients survived for over 1 year and were clinically well at the last examination, with 17, 23, 59 and 78 months after transplantation. In all cases, analyses for CD had negative results.

Discussion

Brazil is presently one the countries with larger numbers of liver transplantations per year. In 2005, 956 transplantations were performed (9). The increased use of OLT, however, resulted as already reported in other countries in an exponential increase in the number of candidates for liver transplantation, and a shortage of available organs. Large waiting lists were thus created, resulting in high mortality indices among patients with terminal liver disease who do not receive a new organ in time.

Transfusional transmission of CD was formally mentioned by Emmanuel Dias as a possible and important public health problem in the Americas (10). In a classical study performed in Argentina, the theoretical risk of infection with one transfusion of 500 mL blood from a person with CD was established as between 12.5% and 25% (11).

In Brazil, around two million individuals are estimated to have the asymptomatic or the usual form of CD (2). Blood from patients with CD is not usually employed in transfusion, due to the risk of transmission of the disease. The Brazilian legislation does not allow the use of livers from patients with any kind of infectious disease without signed authorization from the receptor, so that organs from CD individuals are not in general used for transplantation. Recipients of organs and tissues, in addition, have decreased potential to respond to infectious agents due to the immunosuppressive treatment. The severity of infection is also dependent on other factors, such as the intrinsic virulence of the microorganism, magnitude of the infectious process and susceptibility of the patient. The infected individual may develop acute disease or remain asymptomatic for years, a state in which patients with CD seem to remain for life (2).

The development of CD due to transplantation of a solid organ was first described by Chocair et al. in 1981 (12). In 1993, two cases of acute disease after kidney transplantation were reported in Brazil (13,14). The concern with the existence of the disease in potential donors was stressed after 2001, when transmission of CD to three recipients of organs from the same donor was reported (15). The individuals developed the disease in the postoperative period, and two of them died, one due to secondary complications of acute CD.

The two drugs used for CD, nifurtimox and benznidazole, often cause severe side effects, must be used for long periods, and are ineffective against chronic infection. In acute disease the drugs are effective in reducing the duration and severity of infection but cure is achieved in only about 70% of the cases. In the chronic phase, although parasitemia may disappear in up to 70% of the cases treatment does not alter the serological reaction, cardiac function or progression of the disease (16).

The use of prophylactic treatment in these situations is controversial. In a multicentric study, 117 CD patients submitted to heart transplants did not receive prophylactic therapy. Although the number of patients needing treatment was not described, 0.3% of them died because of the disease (17). In another study, 16 non-Chagasic patients were transplanted with kidneys from CD donors. Prophylactic treatment was not administered, and CD was transmitted to 3 (18.7%) of the receipients, who developed the disease during the first 6 months after transplantation and needed treatment (6).

Barcan et al. reported the development of anti-*T. cruzi* serological reaction, on the 84th postoperative day, in a patient receiving a liver from a donor with CD and who did not receive prophylactic treatment (18). The patient was successfully treated with benznidazole, but the authors concluded that the use of organs from CD individuals should be restricted to emergency situations.

Other studies recommend the prophylactic use of benznidazole. In one of these studies, nine patients were transplanted with kidneys from CD donors and received benznidazole prophylactic treatment. No case of CD was observed among the recipients, in a follow-up of 10 years (7).

A study performed with the support of the Brazilian Health Ministry in 2005 concluded that prophylactic treatment should be given soon after transplantation, in cases where noninfected patients receive organs from infected donors (4). In the present work, we followed these guidelines and administered prophylactic treatment to all the patients.

Most experts concur that treatment should be attempted in all *T. cruzi*-infected patients regardless of clinical status or time of infection. Benznidazole, which is usually available in Brazil, is given as 5 mg/kg/day in divided doses for 60 days. Its side effects include granulocytopenia, rash and peripheral neuropathy. Another drug that can be used is nifurtimox that is given orally, in daily doses of 8–10 mg/kg in four divided doses after meals, for 90–120 days. It generally produces gastrointestinal complaints, weight loss, tremors and peripheral neuropathym (19).

Intolerance to benznidazole was observed in one of the patients included in the present study. Since he developed lung complications and was in the intensive care unit, gastric intolerance could have different causes, and it is difficult to determine if it was due to the use of benznidazole. The drug was well accepted by the remaining patients, and none of them presented serological evidence of infection after the surgery, in spite of the severity of their clinical condition (Child Pugh C) and of the immunosuppressive treatment.

CD is usually diagnosed by parasitologic and serologic methods. In the acute stage, the organism may be found as motile trypanosomes in anticoagulated blood (20), as Giemsa-stained trypanosomes in anticoagulated blood used to prepare thin and thick or buffy coat films (21), or by blood culture or animal inoculation (16). Occasionally, amastigotes can be found in tissue aspirates or biopsies of chagomas or lymph nodes at direct examination, staining or culture. In the chronic stage, however, the organism is rarely found directly but may be detected by culture, animal inoculation or xenodiagnosis. Culture in appropriate media is kept for 30 days, and animal inoculation is done in 3- to 10-day-old laboratory mice or rats (20). In most of the cases, adequate culture conditions take too long to provide the results needed for diagnosis.

Several highly sensitive IgG serologic tests [hemagglutination inhibition, complement fixation, enzyme-linked immunosorbent assay (ELISA), immunofluorescence, Western blot and others] are routinely used and are of presumptive value when positive. However, two or three of these tests should be done because both false-negative (including some cases of depressed immune response) and false-positive tests are common. For the ELISA and immunofluorecense tests, sensitivity is 93–98% and specificity is 99%. Antibodies of the IgM class are elevated early in the acute stage but are replaced by IgG antibodies as the disease progresses. Maximum titers are reached in 3–4 months, thereafter titers may remain positive at a low level for life. In chronic infections when serologic tests are negative, DNA methods sometimes allow diagnosis. These tests may also prove useful in assessing effectiveness of therapy (clearance of parasites), whereas serologic test does not (21). In this group of patients the follow-up was done by hemagglutination inhibition, ELISA and antibodies of IgM and IgG class, following the guidelines of literature to increase the chance of a prompt diagnosis of serological conversion. Cultures were not routinely performed, since none of the patients presented any kind of serological reaction, the method is time demanding and the association of two or three different methods is usually enough for an accurate diagnosis, particularly when patients are serologically examined immediately after transplantation.

It is important to note that seroconversion may be delayed or absent in transplant recipients. Thus, the absence of seroconversion may not indicate the absence of disease. The clinical success of transplanting Child Pugh C type recipients will justify the use of these donors, but it cannot be stated that the recipients have *no* disease based on serology alone.

Parasitemia was investigated 3 and 6 months after transplantation. Results were negative, so that the follow-up included only yearly clinical vigilance and serological testing. Although Cyclosporine and Tacrolimus were used in lower doses than recommended and pulse therapy was avoided as much as possible, no acute cellular rejection was observed in any of the patients. Other studies have suggested the use of the lowest possible immunosuppressive doses, to decrease the risk of reinfection. Bacal et al. observed recidive of CD in up to 75% of patients receiving heart transplantation, during the first year, related to the doses of immunosuppressor used (22).

No reports were found in the literature of liver alteration in CD patients. We observed that the prophylactic treatment with benznidazole was well accepted and effective in transplanted individuals. Taken as a whole, these results suggest that, that in Brazil, where the incidence of CD is high and mortality rates among patients waiting for OLT reach high levels, the use of organs from CD donors for selected patients, with increased risk of death while waiting for a liver, is an important alternative to be considered.

References

1. Secretaria da Saúde do Estado da Saúde—Central de Transplantes (on line). Brasil: Estado de São Paulo; 1998–2004. Disponível em: http://www.saude.sp.gov.br/programas_projetos/transplantes/html/transplantes_dados_mortalidade.html.

2. Moncayo A. Chagas disease: Current epidemiological trends after the interruption of vectorial and transfusional transmission in the Southern Cone countries. Mem Inst Oswaldo Cruz 2003; 98: 577–591.
3. World Health Organization. Control of Chagas disease: Report of a WHO expert committee. Geneva, Switzerland: World Health Organization, 1991.
4. Brazil. Secretaria de Vigilância em Saúde do Ministério da Saúde—Consenso Brasileiro em Doença de Chagas. Rev Soc Bras Med Trop 2005; 38(Suppl III): 4–29.
5. Angelis M, Cooper JT, Freeman RB. Impact of donor infections on outcome of orthotopic liver transplantation. Liver Transpl 2003; 9: 451–462.
6. Riarte A, Luna C, Sabatiello R et al. Chagas' disease in patients with kidney transplants: 7 years of experience 1989-1996. Clin Infect Dis 1999; 29: 561–567.
7. Carvalho VB, Sousa EF, Vila JH et al. Heart transplantation in Chagas' disease. 10 years after the initial experience. Circulation 1996; 96: 2744–2745.
8. Souza AA, Lobo MC, Barbosa RA, Bello V. Chagas seropositive donors in kidney transplantation. Transplant Proc 2004; 36: 868–869.
9. Associação Brasileira de Transplante de Órgãos—ABTO. Registro Brasileiro de Transplantes (RBT) 2005; XI: 9.
10. Dias JC. A doença de Chagas e seu controle na América Latina: uma análise de possibilidades. Cad Saúde Pública 1993; 9: 201–209.
11. Cerisola JÁ, Rabinovich A, Alvarez M, Di Corleto CA, Pruneda J. Enfermedad de Chagas y la transfusión de sangre. Boletin de la Oficina Sanitaria Panamericana 1972; 73: 203–221.
12. Chocair PR, Sabbaga E, Amato Neto V, Shiroma M, Goes GM. Kidney transplantation: A new way of transmitting Chagas disease. Rev Inst Med Trop São Paulo 1981; 23: 280–282.
13. Ferraz AS, Figueiredo JFC. Transmission of Chagas' disease through transplanted kidney: Occurrence of the acute form of the disease in two recipients from the same donor. Rev Inst Med Trop Sao Paulo 1993; 35: 461–463.
14. Faria JBF, Alves G. Transmission of Chagas' disease through cadaveric renal transplantation. Transplantation 1993; 56: 1583–1584.
15. Centers for Disease Control and Prevention (CDC). Chagas disease after organ transplantation—United States, 2001. MMWR Morb Mortal Wkly Rep 2002; 51: 210–212.
16. Rodrigues Coura J, De Castro SL. A critical review on Chagas disease chemotherapy. Mem Inst Oswaldo Cruz 2002; 97: 3–24.
17. 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: 1833–1838.
18. Barcan L, Luna C, Clara L et al. Transmission of *T. cruzi* infection via liver transplantation to a nonreactive recipient for Chagas' disease. Liver Transpl 2005; 11: 1112–1116.
19. Urbina JA. Chemotherapy of Chagas disease. Curr Pharm Des 2002; 8: 287–295.
20. Meneghelli UG. Chagasic enteropathy. Rev Soc Bras Med Trop 2004; 37: 252–260.
21. Salomone OA, Basquiera AL, Sembaj A et al. *Trypanosoma cruzi* in persons without serologic evidence of disease, Argentina. Emerg Infect Dis 2003; 9: 1558–1562.
22. Bacal F, Silva CP, Bocchi EA et al. Mychophenolate mofetil increased chagas disease reactivation in heart transplanted patients: Comparison between two different protocols. Am J Transplant 2005; 5: 2017–2021.