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Recommendations for management of Chagas disease in organ and hematopoietic tissue transplantation programs in nonendemic areas☆

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Abstract

The substantial immigration into Spain from endemic areas of Chagas disease such as Latin America has increased the number of potential donors of organs and tissues. In addition, an increasing number of patients with advanced Chagas heart disease may eventually be eligible to receive a heart transplant, a universally accepted therapeutic strategy for the advanced stages of this disease. Therefore, it is necessary to establish protocols for disease management. This document is intended to establish the guidelines to be followed when a

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potential donor or a tissue or organ recipient is potentially affected by Chagas disease and summarizes the action criteria against the possibility of Chagas disease transmission through the donation of organs, tissues, or hematopoietic stem cells and aims to help professionals working in this field. A single registry of transplants in *Trypanosoma cruzi* infected donors and/or recipients will provide and disseminate experience in this area, which has shown a low recorded incidence to date.

1. Introduction

American trypanosomiasis or Chagas disease is a major public health problem in Latin American countries. It currently affects 8–10 million people, and it has been estimated that 40 million are at risk of contracting the infection [1,2].

Trypanosoma cruzi (T. cruzi) can be transmitted through triatomine vectors, vertical transmission, blood products, infected tissues or organs, and orally. Vertical transmission and transmission through blood products, infected organs and tissues are possible in non-endemic areas. In fact, in Europe, there have been several cases of vertical transmission of *T. cruzi* [3,4], and of transmission through infected tissue or blood products [5-7]. The need for organs and the increase in the number of potential donors from countries where the disease is endemic made us reconsider the evaluation and acceptance of patients infected by *T. cruzi* as both potential organ donors and recipients.

Acceptance or rejection of a donor with positive serology for *T. cruzi* is a controversial issue because of the possibility of transmitting the disease to an immunosuppressed recipient whose treatment can have side effects. On the other hand, rejecting organs or tissues that are useful or vital to people in need may be considered as unethical and jeopardize the patient's life, especially if there are no alternatives and if tools are available for evaluating and monitoring the potential impact of *T. cruzi* in the recipient.

Drug-induced immunosuppression during the transplantation process increases the risk of reactivation of the disease in patients previously infected with *T. cruzi*, which has been reported to occur in between 10% and 75% of cases [8-10]. Patients infected with *T. cruzi* are at risk for short-term infection reactivation, and—although it has not been described—in the long term, the progression of the infection could end in a symptomatic chronic disease with heart, digestive, or other damage [11,12]. The potential risks for the seronegative *T. cruzi* recipient receiving an organ or blood stem cells from a seropositive *T. cruzi* donor are the transmission of the parasite, an acute infection with *T. cruzi*, and possibly a chronic *T. cruzi* infection.

Reactivations have been mainly reported in cases of transplantation of hematopoietic progenitor transplantation (HPT), especially allogeneic and cord blood transplantations (40% of relapses) [13]. Less commonly, reactivation has been reported in solid organ transplantation (SOT), especially of the heart and kidney [13,14]. According to a number of transplants performed in Argentina, transmission through a positive transplant was 18.7% in negative kidney recipients [13].

In addition, as Chagas is a usually asymptomatic chronic disease with a long latency period, patients awaiting an organ or tissue (and the doctors in charge of them) are often unaware of its existence, so it is necessary to implement active screening strategies for potential recipients.

In recent years, the substantial immigration into Spain from endemic areas of Chagas disease such as Latin America has increased the number of potential donors of blood and blood products [15] and also of organs and tissues. Foreign citizens represent approximately 12% of the current Spanish population. Upon arrival in Spain, this population has access to health care, so donation is considered as a possibility for them. Thus, the number of foreign organ donors has been steadily increasing in Spain over the last decade, representing 8.4% of all donations in 2007 (Fig. 1). Organ donors from Latin America represent one third of all non-national donors and the donation rate of Latin Americans is similar to that of the Spanish population.

In addition, an increasing number of patients with advanced Chagas heart disease are being diagnosed and treated in Spanish hospitals [16] and may eventually be eligible to receive a heart transplant, a universally accepted therapeutic strategy for the advanced stages of this disease [8]. Finally, an undetermined percentage of people with chronic Chagas disease (symptomatic or asymptomatic, diagnosed or undiagnosed) living in Spain may also have other pathologies treatable by organ or tissue transplantation. All these premises make it necessary to create a protocol for the evaluation and acceptance of patients infected by *T. cruzi* as potential donors or transplant recipients.

Chagas is an emerging disease in Europe and Spain and is often unknown to health professionals. Therefore, it is

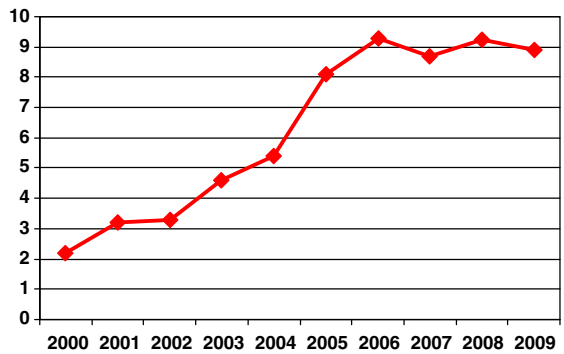

Fig. 1. Trend of the percentage of donors not born in Spain.

necessary to establish protocols for disease management. So far, the Spanish Society of Tropical Medicine and International Health has developed and published 3 consensus documents: one related to diagnosis [17] and the other 2 related to the management of cardiac and gastrointestinal involvement of the disease [18,19].

This document is intended to establish the guidelines to be followed when a potential donor or a tissue or organ recipient is potentially affected by Chagas disease.

2. Chagas disease

2.1. Epidemiology

Migration from Latin America has caused substantial changes in the epidemiology of Chagas disease. Initially, it was a disease linked to poverty and rural areas of Latin America. However, today, it has also become an urban disease due, first, to migration from rural areas to the cities within Latin America and, second, to migration to nonendemic areas such as Europe and North America. Table 1 shows the estimated prevalence of Chagas Disease in endemic countries [1].

Spain currently has more than 2 million residents from endemic areas of Latin American, and it has been estimated that between 47 000 and 67 000 of them are infected with *T. cruzi* [20]. Table 2 shows estimated prevalence of Chagas Disease among different European Countries. One study has shown that a high percentage of people from Latin America suffer from Chagas in one of its clinical forms [16]. To a lesser extent, the disease is also evident in other European countries [23,24].

Table 1
Estimated prevalence of infected patients in 2005 in endemic areas (modified from Ref. [1])

Country	Estimates of infected individuals/percentage of total population
Argentina	1 600 000 (4.1%)
Belize	2000 (0.7%)
Bolivia	620 000 (6.8%)
Brazil	1 900 000 (1.0%)
Chile	160 200 (1.0%)
Colombia	436 000 (1.0%)
Costa Rica	23 000 (0.5%)
Ecuador	230 000 (1.7%)
El Salvador	232 000 (3.4%)
Guatemala	250 000 (2.0%)
Honduras	220 000 (3.1%)
Mexico	1 100 000 (1.0%)
Nicaragua	58 600 (1.1%)
Panama	21 000 (0.01%)
Paraguay	150 000 (2.5%)
Peru	192 000 (0.7%)
Uruguay	21 700 (0.7%)
Venezuela	310 000 (1.2%)
TOTAL	7 694 500

Table 2
Estimated number of migrants infected by *T. cruzi* living in non-endemic countries

Country	Estimated number of infected migrants
United States	300 167
Spain	47 738–67.423
Italy	4337–4610
Japan	3592
France	895–2 619
Canada	1789
Australia	1392
United Kingdom	1006–1324
Sweden	1076–1160
Switzerland	830–1010
Germany	935
Portugal	761–775
Austria, Belgium, Denmark, Greece, the Netherlands, Norway	<500

Data for Australia, Canada, EUA, Japan, and Spain from Ref. [20]; for France, from Ref. [21]; and for other European countries, from Ref. [22].

2.2. Clinical presentation and disease progression

Patients infected with *T. cruzi* who do not follow a treatment during the first months after contracting the infection (the acute form, which usually goes unnoticed) enter into an initially asymptomatic chronic phase, called indeterminate. After 20–30 years, 20–30% of these patients develop cardiac complications (the cardiac chronic form); 10–15%, digestive disorders (the digestive form) or both (the mixed form); and less than 5%, a neurologic form. The rest remain permanently in the indeterminate form without clinical symptoms [25,26].

During the chronic phase, if the patient is secondarily immunosuppressed due to chemotherapy or other immunosuppressive drugs, infections, or malignancies, there is a risk of disease reactivation. The presence of blood parasites detectable by direct methods is considered as a reactivation of Chagas and may or may not be accompanied by typical clinical manifestations of the acute phase of the disease in a patient with chronic infection such as fever, myalgia, hepatosplenomegaly, meningoencephalitis, myocarditis with signs of heart failure, and/or skin lesions. The most common cutaneous signs are nodules and morbilliform and erythematous rash with possible itching. More unusual, and usually related to a late diagnosis, is the appearance of vesicles or bullae with a high parasite load in the interior (chagoma). The clinical presentation in immunocompromised patients is more severe, and the best prognosis is associated with diagnosis and early treatment. In transplanted patients, reactivation episodes are described mainly during the 7–9 weeks post-transplant [27].

2.3. Diagnosis of infection by T. cruzi and Chagas disease

The diagnosis of Chagas disease during the chronic phase according to international standards has been detailed in 2 consensus documents [13,14] and a review [28].

To diagnose the infection by *T. cruzi*, the patient should show:

- ➢ A compatible epidemiological history (see Table 3)
- ➢ Positive serological/parasitological tests

Immunocompetent patients

The patients must show 2 positive results from 2 assays in which different antigens have been used. In case of doubt or disagreement between them, a third technique must be used.

Immunocompromised patient

In patients who have received or are receiving immunosuppressive drugs or who are immunosuppressed, the serological tests for antibody detection may be negative, as has been demonstrated on several occasions [29,30]. Therefore, in immunocompromised people with historical epidemiological risk of infection by *T. cruzi*, it is advisable to perform parasitological tests if the serological tests are negative.

The parasitological diagnosis can be made through the following:

- *Direct methods of parasitological diagnosis:* the Strout method [31] or microhematocrit.
- *Indirect methods of parasitological diagnosis:* hemocultures [32].
- *Techniques based on nucleic acid detection* such as polymerase chain reaction (PCR). Real-time PCR has shown a higher sensitivity than that provided by traditional methods (Strout method, microhematocrit, or hemoculture) even in immunocompromised patients [33,34], so it is currently the technique of choice.

In patients with signs or symptoms of reactivation, parasitological tests may be performed on samples from skin lesion biopsy or endomyocardial biopsy or on cerebrospinal fluid (CSF).

3. Attitude towards potential donor assessment in non-endemic areas

Because of the limited availability of organs for transplantation, we need to consider as potential donors those patients who have an epidemiological history indicating infection with *T. cruzi* and/or positive serological tests. If we have a potential donor or a transplant recipient with unknown serology for Chagas disease, we need to perform an individualized screening based on the presence or absence of epidemiological risk factors for *T. cruzi* infection (Table 3) through the patient's medical history, their relatives, or their close friends. In cases of doubt, when this information is not available or is impossible to obtain, it is advisable to carry out specific serological tests. Because of the nature of the decision making inherent to the process of donating/receiving transplants, every transplantation center could require a rapid serological test for Chagas disease. The test must be validated with a high sensitivity. It should not require expert staff, and the result should be available rapidly and later confirmed by at least 2 specific serological techniques [35].

Table 3
Epidemiological risk factors for Chagas disease transmission that define the need for monitoring

1. Native population from endemic areas (continental Latin American countries).
2. Population who have received a blood transfusion in endemic countries.
3. Offspring of mothers who are native from an endemic country and have a positive or unknown serology for Chagas.
4. Population who have lived in an endemic area for more than one month.

4. Exclusion criteria for transplantation

A kidney transplantation study shows that the percentage of transmission from *T. cruzi* –infected donors to uninfected recipients was 18.7% [36]. According to 2007 data from the Instituto Nacional Central Único Coordinador de Ablación e Implante de Argentina, the prevalence of *T. cruzi* –infected donors was 4.82%. In transplant candidates, the percentage of infection with *T. cruzi* was between 2% (for kidney recipients) and 8.9% (for heart recipients). When the donor is infected with *T. cruzi*, informed consent of the recipient must be obtained.

Table 4 describes the criteria of the World Health Organization (WHO) for acceptance or rejection of organs for SOT, hematopoietic stem cell transplantation (HSCT), and transplantation of any other tissues. The following situations may occur:

4.1. Recipients with T. cruzi infection/Chagas disease

1. Patients with terminal chagasic cardiomyopathy are heart transplant candidates [38,39].
2. Patients infected with *T. cruzi* in the indeterminate phase or initial chronic phase (myocardiopathy grade 0–1 according to the Kushnir classification) (Table 5) may receive a SOT.
3. Patients in the indeterminate phase or early chronic phase may receive either allogeneic or autologous HPT.
4. With the exception of heart transplantation, patients with Chagas disease and myocardiopathy grade 2 or greater according to the Kushnir classification are excluded as transplant recipients.
5. The presence of megaesophagus or megacolon in an advanced stage is a contraindication for any type of transplant.
6. Patients with advanced myocardiopathy and terminal failure of another organ (eg, heart or kidney) may be eligible for simultaneous transplantation of the heart and other organs. The timescale of simultaneity for the transplantation of more than one organ in patients with

Table 4
Criteria for acceptance or rejection of organs depending on serological Chagasic status for both, donor, and recipient (WHO-modified document [37])

Organs	Donor	Recipient	Acceptance	Consent [a]
Kidney	+	+	Yes	Yes
Living and	+	−	Yes[b]	Yes
cadaveric donor	−	+	Yes	No
Liver	+	+	Yes	Yes
Living and	+	−	Yes[c]	Yes: urgency[d]
cadaveric donor				No: elective
	−	+	Yes	No
Lungs	+	+	Yes[c]	Yes
	+	−	Yes[c]	Yes: urgency[d]
				No: elective
	−	+	Yes	No
Heart	+	+	No	No
	+	−	No	No
	−	+	Yes	No
Small bowel	+	+	No	No
	+	−	No	No
	−	+	Yes	No
HTP[f]	+	+	Yes	No
	+	−	Yes[b]	YES
	−	+	Yes	No
Tissues[e]	+		No	

[a] Consent means "recipient informed consent."
[b] When there is no other option.
[c] According to the WHO, an organ for transplantation in patients infected with *T. cruzi* can be accepted in cases of urgency. When organ transplantation is elective, it is advisable to reject the organ from a patient infected with *T. cruzi*. However, in the absence of conclusive data, the final decision will be taken by the transplantation team.
[d] Consent is only required for urgency cases. When organ transplantation is elective, consent is not necessary.
[e] According to national and international standards, all tissues must be excluded. The experience with tissue transplantation is minimal. The number of uninfected tissue donors is sufficient to meet the demand, so we will avoid the risk of potential transmission by excluding tissues from infected donors.
[f] Hematopoietic progenitor transplantation.

Chagas disease is regulated by the same criteria as in patients not infected with *T. cruzi*.

4.2. Living donors infected with T. cruzi and uninfected recipients; exclusion criteria for donation and antiparasitic treatment

A relevant serological and parasitological test will be performed. For hematopoietic progenitor transplantation (HTP) or cell therapy, a donor will only be accepted for an allogeneic transplantation, only when another compatible donor would not be available. For any other transplants, each center can decide its policy for accepting organs from positive donors to be transplanted in negative recipients.

Predonation treatment is recommended for donors infected with *T. cruzi* [40]. However, in cases of maximum urgency, not following the treatment does not preclude donation.

4.3. Deceased donors infected with T. cruzi and uninfected (seronegative) recipients

There is little experience in cardiac transplantation from donors infected with *T. cruzi* [41]. Recently, there have been 2 cases in the United States, in which both recipients died [42]. The heart and the intestines are potentially the organs most affected by the infection, so they should exclude these for transplantation because of the possibility of transmission and the fact that the organ itself may be affected because detection is not always possible. For the remaining organs, transplantation will be possible subject to the informed consent of the recipient and the requirements laid down in Table 3.

5. Evaluation criteria for transplant candidates

According to current legislation, every patient on the waiting list having risk factors for Chagas disease should be submitted to a serology test (see Section 2.3). If, for whatever reason, the patient is immunocompromised and serological tests are negative, parasitological tests need to be done (see Section 2.3). Because of the low efficiency of current antiparasitic treatment to eradicate *T. cruzi* [43], serological and parasitological tests must be carried out even in those patients who have previously received it.

6. Post-transplant monitoring of patients receiving an organ from an infected donor or those previously infected with *T. cruzi*

A Brazilian study shows that the survival rate of heart transplant patients with Chagas disease is higher than that of patients transplanted due to other etiologies (such as ischemic heart disease and idiopathic dilated myocardiopathy), despite the higher risk of neoplasia that was detected in some previous studies [38,39]. This increase in neoplasia has not yet been confirmed by other authors [40]. The same

Table 5
Kuschnir classification of chagasic cardiomyopathy

Group 0: reactive serology, normal ECG, normal chest x-ray or echocardiogram without dilatation of LV
Group 1: reactive serology, abnormal ECG, normal chest x-ray or echocardiogram without dilatation of LV.
Group 2: reactive serology, abnormal ECG, chest x-ray or echocardiogram showing dilated LV, with no clinical or radiological heart failure.
Group 3: reactive serology, abnormal ECG, chest x-ray or echocardiogram showing dilated LV, heart failure.

ECG indicates electrocardiogram; LV, left ventricle.

authors also found a lower incidence of graft vascular disease and low mortality due to reactivation of Chagas disease, despite the frequency of diagnosed reactivations [44].

The incidence of reactivation in recipients with Chagas disease varies according to the transplanted organ and the intensity of immunosuppression [40]: 21% in kidney transplantation [36], 17–40% in HPT [40], and 26.5–75% in heart transplantation [45,46]. Few data are available on liver and lung transplants, but *T. cruzi* transmission has also been reported in some cases [11,47,48].

When a patient infected by *T. cruzi* has received a transplant, or when an uninfected patient has received an organ from a person infected with *T. cruzi*, a periodical evaluation is required to detect the progression of the disease. In HPT candidates, it is recommended to initiate the monitoring of possible reactivation in the chemotherapy phase previous to transplantation.

6.1. Follow-up schedule

It is proposed to carry out frequent parasitological studies (quantitative PCR, Strout method, direct parasitological tests, etc, according to the possibilities of the laboratory), basal pre-transplant and weekly checks for 2 months, bimonthly between the second and sixth months post-transplant, and annually thereafter. However, if there are symptoms, it is advisable to do weekly checks. In cases of febrile syndrome of unknown etiology, urgent parasitological screening must be carried out, followed by suitable treatment if the results are positive.

6.2. Reactivation with or without clinical manifestations

The reactivation of Chagas disease in patients with depressed cellular immunity was described during the 1960s [49] and was defined as a parasitemia increase that may be detectable by direct parasitological techniques even in the absence of symptoms. The appearance of symptoms in these patients represents a worsening and an exacerbation of the underlying disease.

More cases were later described during the arrival of the HIV-AIDS pandemic and the increase in the number of transplants [30,45,50,51]. The symptoms of reactivation or infection may appear late (between the second and sixth months) during the post-transplant phase [27,52], as has already been described in published cases [11,53].

Among transplanted patients, the most common symptoms of reactivation of Chagas disease are subcutaneous nodules (chagoma), panniculitis, myocarditis with signs of heart failure, fever, meningitis, encephalitis, and stroke [45,54-56]. Other symptoms include fatigue, anorexia, and diarrhea [52].

In addition to the parasitological tests on blood samples (See Section 2.3), according to the individual symptoms of each patient, the same tests must be done on samples from skin lesion biopsy, endomyocardial biopsy (cardiac transplant), or CSF.

6.3. Useful laboratory methods for detecting reactivation or primo-infection

- *Serological tests* are only useful in seronegative patients who have received an organ from a seropositive donor (seroconversion).
- *Parasitological and molecular tests*: the Strout method, microhematocrit, and PCR are the techniques that are currently available. Polymerase chain reaction is currently the most sensitive test for the diagnosis of an acute infection and detection of parasitological reactivation. Several studies have also shown that it becomes positive a few days or weeks before the traditional parasitological tests and before the clinical signs of reactivation [46,57]. However, it should be interpreted with caution in patients with chronic Chagas disease, as it can be positive in immunocompetent or immunocompromised patients with no clinical signs of reactivation. A positive PCR in a previously *T. cruzi*–seronegative recipient must be considered as a diagnosis of primo-infection.
- Real-time PCR also allows a precise quantification of parasitemia, and is more useful in predicting the reactivation of Chagas disease in patients with HIV infection. Recently, a technical methodology that improves the sensitivity and reproducibility of this technique marked an important step towards standardization [34].

6.3.1. Microbiological signs of Chagas reactivation

- The Strout method: a positive result is considered as a sign of reactivation.
- Polymerase chain reaction: a positive PCR in patients with previous negative PCR is considered as a sign of reactivation. If the previous PCR was also positive, an increase in the parasitemia is considered as a sign of reactivation.
- Serology: a patient with previous negative serology is considered as a recent infection with *T. cruzi*.

7. Treatment

7.1. Indications for pretransplant treatment

7.1.1. Living donors

For patients infected with *T. cruzi* a pretreatment with benznidazole is recommended, if possible, for at least 30 days and ideally for 60 days. This treatment aims to reduce the parasitemia of the donor before donation. Due to benznidazole-related adverse events, a careful and strict monitoring of the patients is necessary.

7.1.2. Pretransplant treatment (on the waiting list) of the potential recipient infected with T. cruzi/Chagas disease

Despite the low therapeutic efficacy of current treatments (defined as the eradication of the parasite), some studies indicate that treatment with trypanocidal drugs modifies the

evolution of both indeterminate infection and chronic infection in immunocompetent patients [58]. However, this has not been documented in inmunodepressed patients [12].

The experience with heart transplant recipients infected by *T. cruzi* shows that prophylaxis with specific drugs is not always efficient in preventing reactivation [59]. However, in immunocompromised patients with HIV infection and infection by *T. cruzi* with high parasitemia (quantitative methods), treatment is recommended even without evidence of disease reactivation [60].

Therefore, although it is not possible to make a general recommendation based on evidence, it is considered that the risk of toxicity of trypanocidal treatment is higher than the potential benefit. It is therefore recommended to administer trypanocidal only to candidates with detectable parasitemia (Strout method or PCR) at the moment of evaluation.

7.2. Post-transplant treatment indications and/or prophylaxis

7.2.1. In asymptomatic patients

Some professionals use post-transplant prophylaxis as a common strategy [61] in patients receiving organs from donors with Chagas disease. However, it has been proved that an early treatment of reactivations (*T. cruzi* positive recipients) is highly effective [12,62], so both strategies can be considered [61,63]. Because of this lack of evidence and based on the clinical experience of the working group, we recommend treatment with benznidazole or nifurtimox for patients who have parasitological evidence (Strout method or PCR) of reactivation or primary infection (blood, CSF or tissue biopsy) and/or serological seroconversion (donor+/recipient−). When post-transplant prophylaxis is indicated, it needs to be carried out for 30 days with benznidazole at a dose of 5 mg/kg per day [63].

7.2.2. In patients with clinical manifestation and/or reactivation of Chagas disease

Currently, 2 drugs have been approved for the treatment of Chagas disease: benznidazole (5 mg/kg per day) and nifurtimox (8 mg/kg per day) for 60 days. Benznidazole is recommended as the first choice due to the lower incidence of related adverse events [64]. If there is central nervous system involvement, the duration of the treatment should be extended to achieve a clinical and parasitological improvement as well as an improvement in the imaging tests. Patients who have been treated need to undergo a weekly parasitological test for 4 months from the beginning of the treatment. Afterwards, the post-treatment follow-up is resumed.

It is recommended to suspend the specific treatment in cases of leukopenia (white blood cells <2500 cells/mm^3), and neutropenia (<500 cells/mm^3). Close monitoring is required in cases of <1000 cells/mm^3 and in cases of increase in liver enzymes (aspartate aminotransferase [AST] and alanine aminotransferase [ALT]) to more than three times the normal level. Granulocyte colony stimulating factors (G-CSF) could be used to reintroduce the treatment. In cases of therapeutic failure after a treatment with benznidazole or nifurtimox (evidenced by positive parasitological tests), or in cases of suspension of treatment due to the presence of serious adverse events, we try to reintroduce the medication in a second cycle or to administer an alternative drug.

Posaconazole is a drug approved for the treatment of invasive fungal infections. It has shown not only good results against *T. cruzi* both in vitro and in an experimental animal model [65] but also a good tolerance. However, it may only be taken orally and accompanied by fat-rich food. Until now, there has been only one case of treatment with posaconazole in a patient with Chagas disease and immunosuppression due to systemic lupus erythematosus (SLE) [66]. The clinical trials to test the routine use of posaconazole have not been performed yet. However, in cases of therapeutic failure or serious adverse events and lack of other conventional therapies, posaconazole is the current alternative [67,68].

8. Management of immunosuppression

The adjustment of immunosuppression and the reduction in the dose of cyclosporine resulted in lower rates of Chagas disease reactivation and neoplasias [8]. The introduction of mycophenolate mofetil (MMF) instead of azathioprine as an immunosuppressive agent increased the reactivation of Chagas disease [69]. A study published by Bacal et al [8] shows that the probability of reactivation was six times higher in the group of patients who received MMF in the immunosuppression protocol than in the group who received azathioprine. In a recently published retrospective study, the use of MMF was also associated with an increase in Chagas disease reactivation [45]. Therefore, in relation to the presence or acquisition of *T. cruzi* in the SOT, it is recommended not to use MMF for heart transplantation because MMF immunosuppression is more severe than that of azathioprine.

In heart transplantation, it is advisable not to use antithymocyte globulin induction therapy and to try to avoid the use of MMF or mycophenolate sodium in the maintenance immunosuppressive therapy. They can be replaced respectively by basiliximab or daclizumab (induction) and azathioprine (maintenance). Experimental studies suggest the use of rapamycin an immunosuppressive drug used in organ transplantation that may stop cell growth of *T brucei*. Although there is no evidence of its activity in *T. cruzi*, rapamycin could be an alternative to MMF, ensuring proper immunosuppression and perhaps a decrease in reactivation risk [70].

In reference to other SOTs, there is insufficient evidence to recommend an immunosuppressive strategy for these patients. Extrapolating the experience to heart transplantation, it can be suggested not to use antithymocyte globulin induction and to try to avoid or minimize the use of MMF or mycophenolate sodium in maintenance immunosuppressive therapy.

Similarly, in every SOT, it is recommended to reduce the maintenance immunosuppression to the lowest possible level

during reactivation events. However, considering that the response to the treatment with trypanocidal is generally good, there is no need to expose the patient to the risk of acute rejection or the appearance of graft-versus-host disease in allo-HSCT.

Interactions of immunosuppressive drugs with benznidazole and nifurtimox have not been described (Annex 1). The only interaction described is that of benznidazole and nifurtimox with ethanol.

It is necessary to investigate prospectively the risk of reactivation and/or primo-infection, probably increased, in those SOT protocols that use alemtuzumab (Campath) as the drug to prevent antirejection or to treat rejection and the risk in allo-HSCT patients suffering from severe refractory graft-versus-host disease in which infliximab, antitumoral necrosis factor (anti-TNF), is used as a therapy in an advanced phase of the treatment.

9. Conclusions and recommendations

Considering the increase in the population infected with *T. cruzi* in Spain and other non-endemic countries, there is a higher likelihood of obtaining organs for transplantation from these potential donors and of recipients having the infection. This document summarizes the action criteria against the possibility of Chagas disease transmission through the donation of organs, tissues or hematopoietic stem cells and aims to help professionals working in this field. The working group proposes the creation of a single registry of transplanted patients infected by *T. cruzi* and of patients who have received an organ from a Chagas seropositive donor. The registry will provide and disseminate experience in this area, which has shown a low recorded incidence to date.

All the authors declare that there are no conflicts of interest.

Appendix A. Description of drugs and drug interactions

Benznidazole

Benznidazole is a nitroimidazole with cytotoxic and immunosuppressive activity. It works by covalent binding between nitro reduction intermediates and the DNA, proteins and lipids of the parasite. It activates T lymphocytes and inhibits T-helper lymphocytes. As mentioned above, it is active against *T. cruzi* especially in acute or early stages, and less effective in late chronic phase. In relation to pharmacokinetics, it has a Cmax of 2.2–2.8 mg/L with 100 mg oral dose and a half-life of 12 hours. The protein fixation of Benznidazole is 45%. It has limited oral bioavailability [71]. Interactions with immunosuppressants have not been described, and the only established interaction is that with ethanol.

Nifurtimox

Nifurtimox is a nitrofuran acting through the reduction of the nitro group of the molecule to nitro anion radicals, reacting with molecular oxygen to generate reduced metabolites of it that are highly toxic (superoxide anion, peroxide). *T. cruzi* is deficient in some of the mechanisms of detoxification of oxygen metabolites, particularly hydrogen peroxide and is therefore more susceptible to oxidative stress than cells from vertebrates [72]. It is active against *T. cruzi* especially in the acute or early stages, and less effective in the late chronic phase. In relation to pharmacokinetics, it has a Cmax of 0.75 mg/L with a 15 mg/kg oral dose and a half-life of 3–3.5 hours with a distribution volume of (Vd/f) oral 12.5 L/kg. It has an extensive hepatic metabolism (cytochrome P450, nitro reduction). Renal elimination is 0.5–1%. It has a low bioavailability due to its rapid first-step metabolism [73].

Interactions with immunosuppressants have not been described, and the only established interaction is that with ethanol. It is recommended to administer it under strict medical supervision in patients with a psychiatric history.

Medical interaction of drugs used for immunodepressed patients with Chagas disease

The azole antifungals are synthetic compounds that have in common an imidazole or triazole ring. The third generation triazole derivatives fluconazole, itraconazole, voriconazole, and posaconazole are commonly used in the prophylaxis and treatment of these infections in transplanted patients.

Recently, the efficacy of posaconazole as a treatment of chronic Chagas disease is being evaluated [71]. Posaconazole is administrated orally and its availability improves with food (especially fat-rich food); it has a slow absorption that reaches its maximum concentration at 3 hours, but may reach it at 5 hours when taken with an empty stomach. It is highly bound to plasma proteins (98%), mainly to serum albumin and is widely distributed in the organism. It has linear kinetics and is metabolized in the liver by glucuronidation. Renal elimination is secondary and its metabolites are excreted in feces. The terminal half-life ranges from 15 to 35 hours. It cannot be eliminated by hemodialysis. Although the metabolism is independent of cytochrome P450, it acts as an inhibitor of CYP3A4 and can interact with other drugs that are eliminated in that way. As in the aforementioned azoles, the clinical interactions with the immunosuppressive drugs cyclosporine, tacrolimus, everolimus, and sirolimus need to be taken into account [74,75].

Most relevant aspects of drug interaction

Because its hepatic metabolism, the most important azole-drug interactions occur at the pharmacokinetic level with isoenzymes CYP2C19, CYP2C9, and CYP3A4 of cytochrome P450, so all drugs that are administered jointly and are inhibitors such as antiretroviral protease inhibitors

[76,77] or inducers such as antiepileptic and tuberculostatic retroviral reverse transcriptase inhibitors [78,79] may interact to increase or decrease their plasma concentrations and affect both the efficacy and the incidence of toxicity. In addition to being substrates, azoles are inhibitors of the above isoenzymes so drugs administered in transplant patients such as immunosuppressants [80,81], statins [82,83], antiretroviral drugs, and macrolide antibiotics that are metabolized by this route may reach increased concentrations, leading to adverse effects and toxicity.

In the case of immunosuppressants, this is a reason for a significant reduction in the dose of these drugs (cyclosporine, tacrolimus, sirolimus, and everolimus) to remain within the therapeutic range. Sometimes the treatment needs to be withdrawn temporarily to avoid the appearance of toxicity in patients receiving both types of drug. We must be aware that such interactions depend on concentration, so any change in the dose of an immunosuppressant will lead to a change in its concentration (which will interact at different levels with azole antifungal drugs). These patients therefore require close pharmacokinetics monitoring to prevent ineffective therapy and improve the safety of the treatment.

Unfortunately, nothing has been reported concerning interactions at a pharmacodynamic level. However, we cannot rule out interactions that can give rise to synergism or antagonism between antifungal agents and immunosuppressive agents. As a summary, patients should be closely monitored and the administered dose should be personalized in cases of associated toxicity and/or therapeutic failure of the drugs.

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