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Cell therapies for Chagas disease

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Abstract

In this review of cell therapies in Chagas disease, we cover aspects related to the disease, its treatment and world demographics, before proceeding to describe the preclinical and clinical trials performed using cell therapies in the search for an alternative therapy for the most severe and lethal form of this disease, chronic chagasic cardiomyopathy.

Key Words: *bone marrow cells, cardiomyopathy, cell therapy, Chagas disease, mesenchymal stromal cells*

The disease

Chagas disease was discovered in 1909 by the Brazilian physician Carlos Chagas. It is caused by the protozoan parasite *Trypanosoma cruzi*. This parasite is transmitted by hematophagous insects from the Triatominae subfamily, commonly known as kissing bugs. There are more than 130 different species in this subfamily that can be found across the American continents, including South America, Central America, Mexico and most parts of the United States. In Brazil, the most common vector for Chagas disease is *Triatoma infestans*. These insects are usually found in cracks and holes of substandard housing, which are common in rural areas of Latin America. They have nocturnal habits, and the parasite is transmitted by their feces. After feeding, the kissing bug usually defecates and the host tends to scratch the area, introducing the parasite into the blood stream through the bite wound [1–3].

The efforts to control the insect population in Latin America have been successful in reducing the transmission of Chagas disease through the vectorial route. However, non-vectorial forms of transmission are also possible, such as transfusions, congenital (i.e., from mother to infant), organ transplantation, accidents in research laboratories and oral. The importance of foodborne transmission (insects containing the parasite are crushed in the preparation of non-industrialized beverages) has increased in the past decade because there have been outbreaks of acute infection with more severe symptoms and higher mortality [1–3].

Chagas disease has two distinct phases: acute and chronic. The acute phase includes an incubation period of 1 to 2 weeks and lasts 4 to 8 weeks. It is usually asymptomatic but can also present with mild unspecific symptoms, such as fever, fatigue, malaise, joint pain and headaches, making it difficult to diagnose. The presence of entry point signs, called "inoculation chagomas," are typical of vectorial transmission and can help with the diagnosis. Death can occur in this phase as a consequence of severe myocarditis or meningoencephalitis, although this is uncommon (0.25% of cases) [1–3].

After symptoms of the acute phase resolve, the indeterminate period of the chronic phase begins, and patients can remain asymptomatic for decades. Most of these patients (60–70%) will remain in the indeterminate period for the rest of their lives, never presenting any other symptoms of Chagas disease. However, after 10 to 30 years, 30–40% of infected individuals will develop one of three chronic disease forms: cardiac, digestive or cardiodigestive. The cardiac form is the most common, affecting 20–30% of infected patients, whereas the digestive and cardiodigestive forms will affect approximately 10% [1–3].

The cardiac form, usually referred to as chronic chagasic cardiomyopathy (CCC), manifests as three

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syndromes that can co-exist: cardiac arrhythmias, heart failure (HF) and thromboembolism. In the case of arrhythmias, early stages tend to be asymptomatic, and abnormalities are detected only in electrocardiographic exams. Conversely, in late stages, they can be quite severe and life-threatening. In fact, approximately 60% of deaths in chagasic cardiomyopathy are caused by arrhythmias. HF is characterized by an enlargement of the ventricular cavities and global systolic dysfunction. Apical aneurysms may also be present. HF is the second most common cause of death, corresponding to 30% of the cases, and has serious impacts on the patient's quality of life. Symptoms are similar to HF due to other causes, including shortness of breath, fatigue, intolerance to exercise, liver enlargement and swelling of the inferior limbs. Thromboembolism accounts for the remaining deaths and symptoms will depend on the site of embolism. The brain is the most common site, causing strokes, followed by limbs and lungs [1–3].

The digestive form is characterized by the formation of "megas," which are severe enlargements of the esophagus and colon. Megaesophagus causes dysphagia, odynophagia, epigastric pain and regurgitation. Patients can become malnourished if swallowing is severely impaired, and the disease is associated with an increased risk of cancer. Megacolon causes severe constipation and abdominal distention and can frequently be complicated by bowel obstruction due to failure to pass stool [1–3].

Chagas disease requires laboratory diagnosis. During the acute phase, it is characterized by an increased parasitemia (number of parasites per milliliter of blood) and absence of anti–*T. cruzi* antibodies. The gold standard method for the diagnosis during this phase is a direct parasitologic examination, which is based on the microscopic detection of trypomastigotes in blood samples. In the chronic phase, parasitemia recedes and parasites are not usually detected in blood samples. Patients undergo seroconversion and the method of choice for diagnosis is the detection of anti–*T. cruzi* antibodies by at least two of the following methods: enzyme-linked immuno-sorbent assay, indirect immunofluorescence and indirect hemagglutination [1–3].

After the laboratory diagnosis is confirmed, it is necessary to define the clinical form of the disease. A 12-lead electrocardiography examination (ECG) and clinical investigation of digestive symptoms is recommended. If patients are asymptomatic and ECG is normal, they should be reevaluated every 1 to 2 years. If ECG is normal but patients have digestive symptoms, imaging evaluation and assessment of the need for symptomatic or surgical treatment should be undertaken. If ECG is abnormal, chest radiograph, echocardiography and 24-hour Holter monitoring should be conducted for risk stratification [4] (Figure 1).

Risk stratification is an important predictor of prognosis. The mortality in 10 years for low-, intermediate- and high-risk patients is 10%, 44% and 80%, respectively. In the acute phase, prognosis is generally good, except in the case of myocarditis or meningoencephalitis, especially in children. Patients in the indeterminate period have survival and prognosis similar to individuals without the disease [4].

Treatment of chagas disease

Trypanocidal drugs

Two trypanocidal drugs exist in the market: Nifurtimox and Benznidazole. The side effects of these drugs can be quite serious. The World Health Organization recommends that only a physician with experience in managing the drug and who can diagnose and treat side effects should prescribe them. Nifurtimox causes severe anorexia and weight loss (more than 50% of the cases), abdominal pain, nausea, vomiting, headaches, dizziness, mood changes, insomnia, muscle pain and decreased short-term memory. Benznidazole can cause severe skin reactions, paresthesia, anorexia and weight loss, nausea and vomiting. Both drugs can cause peripheral neuropathy, usually characterized by tingling or pain in the lower limbs. This is a dose-dependent and late side effect that requires discontinuation of the drug. Leukopenia or thrombocytopenia are rare but serious and also require discontinuation of the treatment [4,5].

Despite this multitude of side effects, trypanocidal drugs are effective and recommended in specific disease settings. In the acute phase, it is recommended for all patients, except during pregnancy and can cure the disease in 60–85% of the cases. There is also consensus on the treatment of children in the chronic phase. Independent Brazilian and Argentinian clinical trials [6–8] have demonstrated that Benznidazole treatment in children results in negative anti-*T. cruzi* serologies, although data on the treatment's impact on clinical prognosis are still lacking. The third consensual indication for trypanocidal treatment is reactivation of the disease in the chronic phase, which can occur during pharmacological immunosuppression of transplanted patients or HIV co-infection. In the case of adult patients with the indeterminate form of Chagas disease, trypanocidal treatment is also suggested by most guidelines, although no randomized placebo-controlled clinical trials were conducted to support this recommendation [4,5].

On the other hand, according to the BENEFIT trial, patients with symptomatic CCC should not be treated with trypanocidal agents [9]. This trial studied 2854 patients for a period of approximately 5 years