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EDITORIAL

Chagas disease and immunosuppressive therapy: When therapeutic interventions can harm

Enfermedad de Chagas y tratamiento inmunosupresor: cuando las intervenciones terapéuticas pueden causar daño

Over the past decades, immunosuppressive therapy has increased significantly in the clinical practice for the management of autoimmune disorders, hematologic malignancies and transplant recipients. In individuals with chronic *Trypanosoma cruzi* infection, the causative agent of Chagas disease, the onset of immunosuppression can lead to an increase of parasite replication, resulting in elevated parasitic loads in both tissue and circulation. Thus, iatrogenic immunosuppression can trigger parasite reactivation in a similar fashion to HIV/AIDS[1].

Decades after primary infection, one third of individuals with Chagas disease develop damage to target tissues such as the heart and gastrointestinal tract. The rest of *T. cruzi*-infected individuals will remain asymptomatic for life. It is estimated that less than 10% of these individuals are aware of their infectious status. Infected individuals migrate to urban settings within Latin America and to non-endemic regions such as the United States, Europe, Japan or Australia, where they facilitate non-vectorial forms of transmission: mother to child, blood and solid organ donation. Indeed, Chagas disease is globally recognized as an emerging disease[2], gaining attention due to its chronic nature, the end-organ damage it causes and the risk of iatrogenic *T. cruzi* reactivation.

The immune response elicited by acute *T. cruzi* is insufficient for parasite eradication. The parasite persists throughout life mainly in the form of intracellular amastigote nests in tissues and occasional extracellular bloodstream trypomastigotes. Parasite burden is controlled predominantly by cellular immune responses involving Th1 CD4+ and CD8+ cytotoxic T lymphocytes and various cytokines such as interferon-γ, tumor necrosis factor-α (TNF-α), and interleukin-12 (IL-12), but with a certain level of humoral immunity involvement. In addition to the neoplastic and systemic diseases causing immunosuppression, therapies with immunosuppressive drugs can disrupt this immune control, leading to increased parasitemia and clinical manifestations. Reactivation should be redefined as a rise in parasitemia detectable by microscopy or molecular methods, even in the absence of clinical symptoms. While guidelines for monitoring patients undergoing bone marrow or solid organ transplantation are only now being established, the reactivation risk in patients receiving immunosuppressive therapy for systemic autoimmune rheumatic diseases (SARDs) remains poorly studied. There are isolated case reports of reactivation in patients with SARDs and few case series[3].

The treatment of SARDs involves a wide spectrum of immunosuppressive therapies, ranging from corticosteroids to monoclonal antibodies and small molecules targeting specific immune components. Glucocorticoids, for instance, exert various effects on innate and acquired immunity. Non-glucocorticoid immunosuppressive drugs are employed to prevent transplant rejection and treat autoimmune diseases, where they are referred to as disease-modifying antirheumatic drugs (DMARDs). Conventional synthetic DMARDs (csDMARDs), biologic DMARDs (bDMARDs), and targeted synthetic DMARDs (tsDMARDs) are differentiated based on their mechanisms of action[4]. For csDMARDs these mechanisms are diverse or partially understood, they induce cell death or inhibit proliferation (e.g., cyclophosphamide, methotrexate, and azathioprine). Others suppress the immune system by reducing lymphocyte proliferation or function, such as cyclosporine and tacrolimus, which specifically inhibit calcineurin, thereby reducing IL-2 production by activated T cells. Mycophenolate mofetil, which blocks purine synthesis, and leflunomide, which inhibits pyrimidine synthesis, also fall into this category. In contrast, bDMARDs and tsDMARDs target specific molecular components, such as cytokines, their receptors, or cell surface molecules, modulating immune effector mechanisms. bDMARDs, produced by genetically engineered living cells, target key pro-inflammatory effectors such as TNF-α inhibitors, -1 receptor and IL-6 receptor antagonists. Other biologic response mod-

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ifiers are the T-cell co-stimulation blocker, CTLA4-Ig, and the B-cell depleting agent, anti CD20. Targeted synthetic immunosuppressive drugs (tsDMARDs), such as Janus kinase inhibitors are used for different SARDs.

Predicting the risk of reactivation of *T. cruzi* infection of cDMARDS is elusive due to limited understanding of their mechanism of action or to their multiple targets, although evidence could be gathered as many of them have been in use for decades[3]. With regard to DMARDS with defined targets, it should be more feasible to estimate their risk based on the role of their targets in parasite control. However, clinical experience is scarce and new bDMARDS and tsDMARDS are constantly emerging.

For SARD patients with altered immunity, assessing the risk of reactivation is complex, as it depends on the type and intensity of the immunosuppressive regimen. Currently, there is no consensus on monitoring and managing parasitic reactivation. The emergence of new immunosuppressive regimens with enhanced efficacy adds to the complexity, as their risk of *T. cruzi* reactivation remains unknown.

Mortality due to reactivation in immunocompromised patients is primarily due to central nervous system and myocardial involvement. The most common reactivation signs and symptoms include subcutaneous nodules, panniculitis, myocarditis with heart failure signs, fever, meningitis, encephalitis, and stroke. In these cases, preemptive treatment with benznidazole or nifurtimox is effective at controlling parasite load and associated symptoms. Preventive treatment before initiating immunosuppressive regimens has been proposed primarily for patients awaiting a transplant. This approach is the subject of debate as treatment during the chronic phase fails to eradicate the parasite and is not exempt from adverse effects. Thus, proper monitoring of parasitic burden and other reactivation markers seems to be the most appropriate approach[4].

Acute *T. cruzi* infection and reactivation can be assessed by microscopy or by nucleic acid amplification testing in peripheral blood. Yet, *T. cruzi* DNA can also be detected in immunocompetent patients with chronic Chagas disease, thus positive qualitative nucleic acid amplification does not suffice to diagnose reactivation. A rise in parasitic loads reflected by a decrease in cycle threshold (Ct) values (equivalent to parasite concentration in blood) in a quantitative PCR (qPCR) assay is the most reliable indicator of reactivation.

There is no consensus on a clinically relevant definition of asymptomatic *T. cruzi* reactivation to initiate antiparasitic treatment before symptoms appear. Prior to the extended availability of molecular assays, microscopic detection of the parasite in blood, with or without clinical manifestations was the gold standard. In the molecular era, rising parasitic loads detected by qPCR in blood are known to precede symptomatic reactivation by days to weeks[5]. Given the complexities and emerging therapies, ongoing research is essential to refine monitoring and management protocols for this vulnerable patient population.

Worldwide, risk-based testing for Chagas disease should be implemented (i.e., history of residence in Latin America, family history of Chagas disease, maternal or known exposure to the triatomine vector). In Argentina, according to the latest National Chagas Disease Act, screening for *T. cruzi* infection is mandatory for all pregnant women and their newborns, children of infected mothers up to the first year of life and their siblings[6]. Serological controls are also mandatory for donors and recipients of organs, tissues and blood for transfusion. Still, this recommendation does not include assessing Chagas disease status in patients receiving or about to receive immunosuppressive therapy for conditions other than organ or tissue transplants. Additionally, there is a lack of awareness among clinicians regarding the potential risk of *T. cruzi* reactivation in these patients. More evidence should be gathered to stratify the risk of Chagas disease reactivation based on the different immunosuppressive regimens and clinical conditions. Meanwhile, SARD patients receiving immunosuppressive regimens should be screened and monitored with the same frequency as transplant recipients, depending on the type of drug they receive, to prevent reactivations.

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