TUBERCULOSIS IN SOLID ORGAN TRANSPLANTATION: PROSPECTS AND CHALLENGES IN THE BRAZILIAN CONTEXT

Tuberculose em transplante de órgãos sólidos: perspectivas e desafios no contexto brasileiro

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ABSTRACT

The management of tuberculosis (TB) in candidates and recipients of solid organs poses several challenges. Among them, TB diagnosis is often delayed by the atypical presentation of the disease and difficulties related to the anti-TB drugs toxicity and the interaction with immunosuppressive drugs. This review includes relevant articles published in the last 20 years and also takes into account the current Brazilian recommendations for the diagnosis and therapeutic management of TB in solid organ transplant (SOT) recipients. It also attempts to provide useful recommendations to assist physicians as to the patient care, and presents the main limitations for a better approach upon considering the Brazilian scenario.

Keywords: Tuberculosis; Transplantation; Transplant Recipients.

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INTRODUCTION

Tuberculosis (TB) is a rare and severe disease in solid-organ transplant (SOT) recipients. In this special population, TB frequency varies according to the prevalence in the general population and the type of the organ transplant. In Brazil, an endemic area for TB, the prevalence among SOT recipients is still unknown. It is worth mentioning that the incidence of TB in Brazil ranges from low to high, depending on the location. The frequency of the disease may also depend on the socioeconomic level of the population. Brazil presents a specific context with an overlapping between TB endemic areas and the high amount of transplants performed by the public health system. It is particularly noted that Brazil has an effective TB control program, a low rate of primary resistance, and usually, a restricted access to important diagnostic tools available to recognize latent and extrapulmonary TB. Recently, there have been new resources to this approach. A review of these technologies is required for their incorporation into the clinical routine. In the transplant setting, the better the diagnosis and therapeutic management, the higher survival rate for the patient.

Epidemiology

According to the World Health Organization (WHO), in 2012 8.6 million TB cases were diagnosed and reported worldwide, with 1.3 million deaths1. The TB median incidence estimated in Brazil is 46 (38-55)/100,000 inhabitants per year. Despite the decline of such rate over the years, Brazil still ranks among the 22 countries with majority of cases with 81% of cases worldwide.[1,2] These amoubts are still much higher than those found in developed countries, such as the United States and Western European countries, whose overall incidence of TB is below 20/100,000 inhabitants per year, which seen as low incidence.[1]

When considering active TB among patients undergoing SOT, frequency rates vary from 1.2% to 6.4% in most developed countries, reaching up to 15% in highly endemic areas, and the risk is estimated to be 36 to 74 times higher than among the general population.[3,4] These rates also vary according to the organ transplanted,[5] being the lung transplantation that at highest risk. In a Spanish cohort, TB was higher among SOT recipients (512 cases/100,000 inhabitants per year) when compared to the general population IN Spain (18.9 cases/100,000 inhabitants per year), and lung transplantation was at highest risk to development the disease (2.072 cases/ inhabitants per year).[6]

The TB mortality rate in SOT recipients varies from 19-40%, and it might reach up to 10 times the mortality in the general population. The presence of the disseminated disease, previous rejection episodes and the use of immunosuppressants OKT3 or lymphocytes depleting antibodies are associated with a higher risk of death.[4,7] One study [8] presented higher mortality in liver and heart recipients. Another study [5] showed a high mortality rate during treatment (17%) associated with extrapulmonary involvement and secondary hepatotoxicity to anti-TB drugs, which is more common among liver transplanted recipients.

In Brazil, there is a lack of information regarding TB in SOT recipients. Most published works include retrospective analyses and reviews mainly in Kidney transplantation (KT) and Liver Transplantation (LT). Among these works, TB frequency varies from 0.47% to 4.5% (above the index in the general population).[9-14] Despite these studies, a nationwide population-based research focused in epidemiological data is still needed.

Risk factors and transmission

In the transplant setting, there are four possible scenarios for a patient presenting active TB. The reactivation of the latent infection in this patient is responsible for most cases. Donor derived infection, which is the reactivation of the latent infection in the graft can also occur in any type of transplant, being more common in lung transplantation. Reinfection after transplantation is also a possibility, especially in highly endemic areas. After the exposure, the risk for progression to activate the disease is quite high in those patients. Although much rare, some patients may already have the active disease, requiring an urgent transplantation.[7,15]

Increased risk to develop TB in the post-transplant period is related to a history of exposure to the Mycobacterium tuberculosis (MTB) evidenced by the Tuberculin Skin Test (TST) reactivity or compatible radiological abnormalities (untreated). Rejection episodes, presence of diabetes mellitus, advanced age, chronic hemodialysis or kidney disease or infection by hepatitis C (for kidney transplanted patients), chronic liver disease, other infections (deep mycoses, cytomegalovirus disease, Nocardia and pneumocystosis).[15,16] can also increase the risk. Lung transplantation is also an important risk factor for developing TB, which is not surprising, as the lung is the gateway to the bacillus.[6]

Other factors that increase the risk of TB in the general population also apply to transplanted patients (malnutrition, smoking and HIV infection, for example). Among immunosuppressors, the use of Muromonab-CD3 or T lymphocytes antibodies are associated with an increased risk for TB, as well as the need to increase the immunosuppression associated with rejection episodes.[15,16]

Pretransplant assessment

Latent TB infection (LTBI) reactivation in the recipient is the main cause for active TB after transplantation. Guidelines recommend to screen candidates regarding this infection, including careful assessments of the previous exposure of the patient to MTB (home, professional, nosocomial or even trips to places with high local endemicity), past active disease (observing the details of previous treatment as therapeutic regimen and duration) and also LTBI treatment.[17,18]

Radiological evaluation of candidates, searching for sequelae that can act as latent foci is usually done by chest X-ray or Computerized Tomography (CT). Although simple chest X-ray is usually the method of choice, some signs of LTBI can remain unnoticed by this method, and it may be seen only on CT.[19]

The detection of cellular immune response against MTB antigens is frequently used to assess the presence of LTBI. It can be performed by using the Tuberculin Skin Test (TST) or based on the interferon-gamma release assays (IGRA). When compared to TST, IGRA has certain advantages. It has better specificity, as TST can be influenced by prior BCG vaccination or exposure to other Mycobacteria. In addition, there is an operational

advantage, as IGRA is performed in a single visit, whereas TST requires patient return after 48h-72h.[20-22] Presently, there are still few studies comparing these two tests in immunocompromised patients. In conclusion, there is still not enough evidence to recommend IGRA other than TST.[7,23]

It is always important and necessary to exclude active TB in patients with positive TST and/or IGRA. If there is clinical and/or radiological evidence of TB, including residual lesions, fast acid bacilli (FAB) in sputum and culture should be performed, and if this is not possible, bronchoscopy aspirate cultures or bronchoalveolar lavage (BAL) should be performed. In the event of suspicions of extrapulmonary tuberculosis, FAB, culture and histopathological analysis should be carried out. The donor assessment is also very important. In the case of living donors, risk assessment is recommended based on the history of previous exposure to TB and TST or IGRA.[24] In deceased donors, it is not possible to hold TST, but a careful review of their clinical history and possible exposure or contact with MTB should be analyzed. Any suspected active TB should signal to contraindication for the donation of any organ.[15]

Tuberculosis diagnosis

The active disease usually occurs in the first year after transplantation (a 9 months average), except for KT recipients, who gets ill later, due to less immunosuppression.[4] Clinical manifestations of the disease can be atypical or less prominent, which can delay TB diagnosis.16 Although pulmonary disease is the most common presentation (51%), the extra-pulmonary or disseminated involvement is more frequent in transplanted patients than in the general population, reaching up to 16% and 33% cases respectively. Symptoms presented by those patients are usually nonspecific, although fever, night sweating and weight loss are commonly observed.[4]

The prompt diagnosis is essential to prevent poor prognosis and a higher severity of the disease. However, the recognition of TB still fails due to the lack of fast and effective diagnostic tools.[25]

TB diagnosis in SOT is similar to not compromised patients, and it includes: radiological imaging, direct testing for FAB in sputum or other tissues/secretions, culture, histopathology and molecular tests for bacilli detection. Conventional radiography is still the most commonly used screening, diagnosis and monitoring methods in patients with TB. Radiological abnormalities can include focal infiltration (40%), miliary pattern (22%), pleural effusion (13%) and nodules (5%). The cavitation findings are unusual and occur in only in about 4% of cases.[4] Up to one third of patients may have chest X-ray without a significant change. High resolution CT is more sensitive in identifying early parenchymal lesions or mediastinal lymph nodes and in determining the disease activity.[26,27] Suggestive findings are parenchymal abnormalities as centrilobular nodules and tree-in-bud.[28]

Direct microscopy is a simple and safe method but must be performed by a qualified technician. The Ziehl-Nielsen method has to be performed in at least two sputum samples and it is the most commonly used in Brazil. The sensitivity is reduced in transplanted patients, but it is still expected to meet 50% positivity in repeated samples.[29]

Mycobacteria culture is always recommended. It presents a high specificity and sensitivity enabling a further assessment of the resistance profile. In pulmonary TB cases with negative smear, culture can increase diagnosis in up to 30%.[29,30] WHO recommends the use of specific liquid growth medium for the diagnosis, as it improves the detection of TB within a shorter time when compared to traditional solid growth medium.[31]

The increasing incidence of multidrug-resistant (MDR) tuberculosis has been seen worldwide. Even thought Brazilian rates are not too high, there has been an increase over the past years. Primary resistance to isoniazid, for example, increased from 4.4% to 6%. Thus, sensitivity tests become increasingly important.[30]

The Nucleic Acid Amplification Tests (NAAT) for M. tuberculosis are sometimes used to diagnose TB. The NAAT results may be available within one day after obtaining sputum or BAL. However, the amplification goals are not standardized and diagnostic accuracy of the tests are very heterogeneous.[27] In patients with positive sputum, the sensitivity for NAAT to detect M. tuberculosis nucleic acid is higher than 95%.[32-34] In contrast, in subjects with negative FAB, sensitivity of NAAT, it is too heterogeneous to diagnose the active tuberculosis and imprecise to justify its routine use.[35-37] Real-time PCR assay (Xpert MTB/RIF) is another molecular test that produces quick results (≈2 hours), not only in determining the presence of MTB, but also to assess the presence of resistance to rifampicin.[29]

The histopathological examination is very important for extrapulmonary or pulmonary disease with diffuse infiltrates (e.g. miliary TB). In immunocompetent patients, tissue smear is usually negative, and the presence of granuloma with caseous necrosis is compatible with the TB diagnosis. On the other hand, in immunosuppressed patients, these findings are less frequent, but positive bacilli in the biopsy material are usually higher. However, culture is the best method of diagnosis for TB, as it confirms the presence of the bacilli. Therefore, all material obtained by biopsy should also be stored in distilled water or saline solution and sent for culture in a specific medium.[30]

New immune-serological tests have recently become available to detect latent TB. So far, none of those tests has been recommended to diagnose active TB, due to its low performance in highly endemic countries.[38,39] However, the lack of a gold standard test is a limiting factor in the TB detection, and the discovery of new biomarkers for the disease still poses a major challenge.[25]

Treatment of latent and active TB

TB treatment in a SOT candidate or in a post-transplant recipient should take into account the interactions between anti-TB and immunosuppressants drugs, and the risk of the drug toxicity, especially in LT.

LTBI

LTBI treatment in candidates to the transplant should be considered in the following conditions: initial TST or following a positive "booster effect" (≥ 5 mm duration), positive IGRA, previous history of TB incorrectly treated, direct contact with an infected person or residual TB lesions on chest X-ray or CT scan (fibronodular apical lesions, calcified solitary nodule, calcified lymph nodes or pleural thickening) without adequate pretreatment and individuals originated from an area with a very high incidence of TB (> 100 per 100,000 population).[15,24]

Implementation of prophylaxis for high-risk patients is extremely important to reduce the active TB. An interesting study was conducted in Brazilian KT recipients in a high endemicity area (95-115 cases/100,000patient-years). Authors discriminated high-risk patients considering LTBI diagnosis reported a recent contact (previous 2 years) with individuals with TB and recipients who received a graft from a living donor with LTBI. Reduction of TB rates was noted when appropriate prophylaxis was initiated in this population. In this study, the authors considered the risk factors but didn't recommend universal prophylaxis even though there was a high incidence rate of TB in the general population.[40]

A systematic review that studied LTBI treatment efficacy in LT candidates also showed that LTBI treatment can prevent active TB disease in the post-transplant period. Among 238 patients identified as having any pretransplant latent MTB risk factors (positive TST, radiographic abnormality or clinical history), isoniazid LTBI treatment was associated with a reduction in active TB rates.[44]

LTBI treatment rests especially on isoniazid (H), 300mg/daily or twice a week by Directed Observed Treatment (DOT), for nine to 12 months plus vitamin B6 (pyridoxine). For KT only, this regimen is recommended for six months. Alternative regimens include H twice a week for nine months, H daily for six months, rifampin (R) daily for four months, R and H daily for three months, and H and rifapentine once a week for three months. R associated to pyrazinamide (Z) for two months is not recommended, due to its high hepatotoxicity.[41-43] The Centers for Disease Control and Prevention (CDC) and the American Society of Transplantation (AST) preferably recommend nine months of H for LTBI treatment, due to their low liver toxicity and higher efficacy.[45,46] R containing regimens may be considered in patients at risk for LTBI resistant to H and should be used for four months.[24,46] The Brazilian Ministry of Health forebodes that the treatment of LTBI must be performed with H for a minimum period of 6 months. This approach reduces by 60% to 90% the risk of illness. The recommended dose is 5 to 10mg/kg weight, up to a maximum dose of 300 mg/day.[30]

Treatment of LTBI should be performed before the transplantation and the immunosuppressive therapy, as these drugs interact with anti-TB agents. Exception to this recommendation occurs in LT, in which some experts recommend delaying the treatment until the post-transplantation period, after stabilizing the graft function. Such difference is due to the risk of hepatotoxicity linked to anti-TB drugs, which might cause imbalance in patients on the waiting list without availability of organs for transplantation.3,15,16 However, although there is risk of hepatotoxicity, another Brazilian retrospective study observed that it was possible to start isoniazid for LTBI treatment before LT. In this study, there were 27 patients receiving H and in none of them the drug discontinuation was required.[47]

In patients using H, the increase of the serum aminotransferase levels should not be automatically attributed to the drug toxicity. If necessary, a specific diagnosis should be sought through liver biopsy.[18]

Adverse events related to the LTBI treatment should be systematically checked. Laboratory tests (ALT, AST and bilirubin measurement) are recommended every two weeks for six weeks; after that period, they should be monthly performed. The increase from 1.5 to 3 times above the normal value is common and it should not define the suspension of the therapy, but tests should be done more frequently. The discontinuation of the therapy is recommended when the increase is higher than three times the reference value of aminotransferases in symptomatic patients or higher than five times in asymptomatic patients.[7,18] In such cases, it must be sought alternative treatments with ethambutol and quinolones, for example.[15]

TB treatment

Treatment recommendations in transplanted patients are similar to those for the general population.[41] However,

there are three important aspects to be addressed:

- interaction between rifamycins (rifampin, rifabutin or rifapentine) with calcineurin inhibitors immunosuppressants (cyclosporine, tacrolimus), rapamycin and steroids;
- drug toxicity;
- treatment duration.

Rifampin lowers serum concentrations of cyclosporine and tacrolimus; it has been associated, in some studies, with a higher risk for rejection, raising the mortality among this group of patients.[47] Therefore, it is recommended to increase the calcineurin inhibitors dose about 3 to 5 when using R, and also to monitor the immunosuppressive drugs concentrations in these patients.[3,15,48]

Interaction of rifabutin with immunosuppressive drugs is less important and can be used to replace R with the same efficacy and lower risk of graft loss. It is observed that, regardless of rifamycin as part of a system of anti-TB drugs, the risk of recurrence is low when treatment is extended beyond 12 months.[7,48] Rifabutin is available in Brazil, supported by Health Ministry, but its use is linked to cases of TB in HIV-AIDS patients, who need antiretroviral therapy incompatible with R.[30]

Clinically stable patients without severe TB (excluding: central nervous system disease, pericardial, musculoskeletal and disseminated) and no evidence of H resistance can receive a course of treatment without rifamycins. H and Z have been used for 18 months, in transplanted patients, and streptomycin is used in the first 2 months. Due to the risk for hepatotoxicity, a specific monitoring of liver enzymes is especially required in LT recipients. The administration of aminoglycosides in transplanted patients should be assessed with care due to the risk of potentialization of the nephrotoxicity posed by the drugs with calcineurin inhibitors.[15,16]

A Spanish study showed that lower than 9 months treatment duration was associated with an increased mortality.[15,48] In a Korean study, the only factor significantly associated with recurrence of TB in KT recipients was the shortest duration of the treatment.49 Thus, it is recommended that, regardless the presence of rifamycin in the therapeutic regimen, the patient should be treated for at least 12 months.[7,15,49]

The use of fluoroquinolone can be an alternative.[7,50] The new generation fluoroquinolones (moxifloxacin or levofloxacin) can be used as alternative to the oral therapy with first-line agents.[51] The use of moxifloxacin was shown to be equivalent to H in achieving negative culture in the intensive phase of the treatment.[52,53]

The Brazilian Guidelines for Tuberculosis Control [30] does not indicate the specific treatment regimen for active TB patients undergoing SOT. It is recommended to use the basic scheme for all forms of pulmonary and extrapulmonary TB except for meningoencephalitis: RHZE for 2 months (intensive phase) and RH for 4 months (maintenance phase). For meningoencephalitis, the maintenance phase is extended to 7 months. The Brazilian Health Ministry also recommends the discontinuation of the treatment upon the event of hepatotoxicity proven by increasing enzyme levels (three times higher than the normal value with onset of symptoms, or five times higher in asymptomatic patients, or in cases of jaundice). If there is a reduction in the serum levels of liver enzymes and resolution of symptoms after the stopping the treatment, reintroduction of the basic scheme is indicated: R and E, followed by H, and finally, Z, with an interval of three to seven days between them. The laboratory assessment should be performed before adding each drug. If hepatic enzyme will not be reduce to lower than three times the normal upper limit within 4 weeks or in severe cases of TB, alternative drugs become the best option. These schemes indicate replacing some drugs to streptomycin and/or quinolone derivative.

The III Guideline for Tuberculosis of the Brazilian Thoracic Society sets that in transplanted or patients under the use of immunosuppressive, the TB treatment may be extended to 9 months and the follow up should be performed for 2 years after cure.[54]

In a retrospective analysis including 319 patients undergoing LT, seven cases of active TB were observed. This study showed no significant hepatotoxicity with conventional treatment and the survival rate was 100%.[13] Another recent Brazilian study (retrospective cohort) assessed the hepatotoxicity rates in 69 SOT patients with TB. In this study, 33% patients presented liver toxicity. The use of rifampin in 600mg daily doses or higher was found to be an independent risk factor for liver toxicity in SOT recipients.[55] Despite the risk, especially in cases of disseminated disease with high risk of death, a highly efficient regimen is desirable, but patients must be closely observed.

TB treatment in SOT patients is still controversial, especially regarding the disseminated disease, interaction with immunosuppressants, restricted administration routes and high toxicity rates. The choice of the therapeutic regimen should be made individually.

New perspectives to treat TB and LTBI

New drugs in several stages of development may offer better alternatives to treat TB and LTBI. The new-generation fluoroquinolones, such as moxifloxacin, are excellent examples. In the experimental animal model of latent infection, one weekly rifapentine + moxifloxacin dose for 3 months was found to be as effective as the

daily treatment for 9 months with H.[52,53] The PA-824, a nitroimidazo-oxazine, is another promising compound active against MDR-TB strains, and it is also active against non-replicating persistent bacteria, making it ideal to treat LTBI. The treatment regimen containing PA-824, moxifloxacin and Z was highly effective in a murine model of TB.56 The OPC-67683, one-nitroimidazol oxazone is another new compound showing promising outcomes against TB in mice.[57] A diarylquinoline (R207910, also known as TMC207) showed more potent bactericidal activity than H during the early infectious phase and a higher bactericidal activity in late infection stage than R alone and thus, it can provide another option to treat LTBI.[58,59] Another promising drug is the SQ109 (1, 2-ethylenediamine), which is structurally related to E, but it seems to be more potent.[60,61] It is expected that some of these new drugs will be able to provide additional options to treat TB and LTBI in the near future.

Importance of diagnosis and treatment of TB in the Brazilian context

According to the literature, the occurrence of TB in SOT patients in Brazil is in consonance to the rates found worldwide. Variations among countries may be associated with specific endemicity in each region. However, there are still very few publications concerning TB in the transplant setting in Brazil, despite the significant overlapping of TB endemic area and one of the largest public health transplantation services in the world. Thus, it is important to develop systematic studies and research in this area and to increase information exchange between transplanting institutions.

RESUMO

O manejo da tuberculose (TB) em candidatos e receptores de órgãos sólidos apresenta vários desafios. Entre eles, o diagnóstico da TB é frequentemente atrasado pela apresentação atípica da doença e dificuldades relacionadas à toxicidade de drogas anti-TB e da interação com drogas imunossupressoras. Esta revisão inclui artigos relevantes publicados nos últimos 20 anos e também considera atuais recomendações de brasileiros para o diagnóstico e manejo terapêutico da tuberculose em receptores de transplantes de órgãos sólidos (TOS). Inclui-se também recomendações úteis para auxiliar o médico na assistência ao paciente e apresenta as principais limitações para uma melhor abordagem, considerando o cenário brasileiro.

Descritores: Tuberculose; Transplante; Receptores de Transplante

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