Review Article

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TANAFFOS

Tuberculosis in Solid Organ Transplantation

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Active tuberculosis (TB) is one of the major opportunistic infections that may occur in solid organ transplant recipients. Diagnosis and treatment of latent and active TB are challenging in this population due to lack of randomized clinical trials. In this review, we discuss the clinical manifestations of TB, diagnosis of latent TB and treatment of both latent and active TB.

INTRODUCTION

Nine million people are annually infected with TB worldwide and about 2 million of them die each year. Currently, high prevalence of the human immunodeficiency virus (HIV) and TB drug resistance is a global challenge. In addition, the increase in cases of immunocompromised patients susceptible to TB can account for the high rates of TB prevalence. The increasing use of immunosuppressive drugs including different types of biological agents for treatment of various diseases can increase the risk of opportunistic infections such as TB. The majority of solid organ transplant recipients are at high risk of TB due to the lifelong use of immunosuppressive drugs (1-4).

Epidemiology and clinical manifestations

The risk of active TB infection in patients receiving solid organ transplants is about 20 to 74 times higher than that in the general population, depending on the incidence of TB disease in the general population. The incidence of TB in developed countries in renal transplant recipients is 0.5 to 6.5% while this value is reported to be 15.4% in endemic areas (5-7).

The risk of TB incidence also relates to the type of transplantation and the treatment protocol. The recipients of lung transplantation have the highest risk of active TB. In addition to the type of transplantation, anti-T cell antibodies, treatment of graft rejection, chronic renal failure, diabetes mellitus, hepatitis, chronic liver disease and old age all increase the risk of TB (8,9).

Most TB cases occur during the first 6 months after transplantation. Positive tuberculin skin tests (TSTs) or radiographic evidence compatible with old TB are associated with an earlier age of onset. The use of antibodies against T cells is associated with earlier incidence of TB. Most cases occur in pulmonary form (51%). Extra pulmonary and disseminated forms of TB present in 16% and 23% of cases, respectively (10-12).

Clinical manifestations of TB such as cough, fever, night sweats and weight loss are seen in most patients but many patients present with non-specific symptoms. For instance, fever has been reported in 64% of patients with pulmonary TB, while 91% of patients with disseminated TB have fever. In addition, radiographic findings in these patients vary. Focal infiltration, miliary nodule, pleural effusion, disseminated interstitial infiltration and cavitary lesions have been reported in these patients.

Various manifestations of TB are not considered as the primary diagnosis in one-third of patients; 3% to 5% of patients are diagnosed after death (13-14). In addition, the possibility of poorer outcome in this group of patients is higher. Mortality in these patients is approximately 57% to 80% and is directly related to TB. Another important point is the significant interaction of anti-TB and immunosuppressant drugs that cause rejection in one-third of patients (13-16).

Diagnosis and treatment of latent tuberculosis

The diagnosis of latent TB infection is based on 2 laboratory tests, which measure the immune response to mycobacterial antigens including TST and interferon-γ release assay (IGRA).

IGRA tests are done in two ways.

1. Measurement of gamma interferon secreted by T-cell lymphocytes by ELISA (Quantiferon test)

2. Measurement of gamma-interferon-secreting T cells (Elispot)

IGRA methods have practical advantages compared to the skin test methods:

1. These tests could distinguish the false and true positive cases because of the positive and negative controls.

2. Another point is the specificity of IGRA compared with PPD because of specific antigens, which are used in IGRA.

3. In addition, IGRA tests have a higher sensitivity compared with PPD in people who are immunocompromised (17-22).

The risk of TB in patients with transplantation is at its highest during the first year, and the mean time of occurrence of TB is about 9 months post-transplantation (1).

Identification of individuals at high risk of TB before transplantation is very important. Identification of latent TB before transplantation is a priority and both PPD and IGRA are recommended to increase sensitivity (1,18,22).

In addition to the above, identification of high risk cases for active TB is also very important. For this reason, history of contact with TB and presence of suspicious lesions on chest radiographs are very important (1,4). Latent TB is treated by using isoniazid for 9 months. Usage of rifampin is an alternative treatment. However, rifampin has extensive interactions with immunosuppressive drugs and cannot be used after transplantation. The use of rifampin and pyrazinamide is not recommended due to the high risk of hepatotoxicity (1,4,6).

Prevention efforts for TB should be started before transplantation. In some patients, such as those undergoing kidney transplantation, initiation of treatment before transplantation should be considered. However, in some cases, particularly in emergency situations, treatment in pre-transplant period is not feasible so it can be completed after transplantation.

In some types of transplants, including liver transplantation secondary to advanced liver failure, prevention before transplantation is not possible and prophylaxis can be done after liver transplantation (17-22).

Active tuberculosis treatment

Treatment of active TB in transplant patients must be started as soon as the diagnosis is made. Treatment in these patients has two main challenges:

1. Rifampin interacts with immunosuppressive drugs:

Rifampin could decrease the dosage of immunosuppressive drugs by 3 to 5 times and increase the risk of rejection. Therefore, dosage adjustment should be done accordingly.

2. It increases the drug side effects (1-4,23)

Generally, in severe forms of TB, regimens containing rifampin have a higher response rate. Rifabutin could reduce the frequency of drug interactions and can be used safely instead of rifampin (1-4, 23).

In milder cases of TB (lymphadenopathy), rifampicin-free regimens are recommended (isoniazid and ethambutol for 18 months with pyrazinamide for the first 2 months). The duration of treatment for severe TB is recommended to be at least 9 months. Also, if the disease is severe or the organ is useless, reduction of immunosuppressive therapy should be considered (1-4, 23).

CONCLUSION

TB is one of the major opportunistic infections that may occur in solid organ transplant recipients in endemic countries. Diagnosis and treatment of latent TB before transplantation significantly decrease the rate of active TB.

Pre-transplant screening with both PPD and IGRA tests may increase sensitivity for detection of latent TB.

Treatment of TB with rifampicin-containing regimens for longer duration is recommended for severe cases. Usage of rifabutin has lower risk of drug interaction.

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