Original Article

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Treatment of tuberculosis infection complicated with liver transplant

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Abstract: Liver transplant is considered the best choice for treating various end-stage liver diseases either at home or abroad. Among patients of liver transplant complicated with tuberculosis (TB), the incidence and mortality of postoperative active TB are bound to increase remarkably. Diagnosing and treating TB in patients with end-stage liver diseases who received immunosuppressants after liver transplant are difficult because of the absence of specific clinical manifestations while being complicated with TB, reduced sensitivity to cellular immunoassay, and interaction between anti-TB drugs and immunosuppressants. Therefore, the screening of high-risk groups, improvement in diagnostic accuracy, preoperative treatment, and reduced interaction between anti-TB drugs and immunosuppressants can help optimize diagnosis and treatment regimes and thus further improve the prognosis of patients.

Keywords: liver transplant, tuberculosis, LTBI

Tuberculosis (TB) is a serious global epidemic. Based on the *2015 Global Tuberculosis Report* published by the World Health Organization in 2014, the number of new cases worldwide was 9.6 million. Among them, 940,000 new cases were found in China, with an incidence of 0.68%. The incidence of active TB among patients who have undergone a solid organ transplant (SOT) is higher than that of the general population. The incidence of TB is approximately 1.2%–6.4% in developed countries and even up to 12% in areas with a higher prevalence [1], whereas the incidence in China is approximately 1.52%–2.29% [2–4]. The incidence varies with the type of organ transplant [1, 5] with approximately 0.47%–2.3% among patients who have undergone a liver transplant [6–9]. Interactions exist between immunosuppressant and anti-TB drugs because the diagnosis and treatment of TB complications is difficult with liver transplant, wherein the drug resistance of *Mycobacterium tuberculosis* increases as the prevention, diagnosis, and treatment of TB face many problems.

1 Pathogenesis and prognosis

The risk of TB in liver transplant patients is affected by many factors but mainly depends on the prevalence and postoperative immunosuppression in the locality where the donor/recipient lived. The pathogenic pathways of TB after an organ transplant are classified roughly into the following groups: activation of pathogenic bacteria in past carriers of *M. tuberculosis*, primary TB infection (TBI) after transplant, and direct spread by the donor's organ. The first group is the most important cause, that is, latent pathogens of old TB lesions are activated in patients [10]. The second is less likely to occur with only a few cases reported [6, 11], and the third accounts for 5% of all the cases with active TB after an organ transplant [8]. The risk factors for an infection of active TB in SOT patients mainly involve [1, 5] whether the patients are aged, AB blood

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type, non-white, or complicated with other diseases, such as chronic renal failure, hematodialysis, chronic liver disease, diabetes mellitus, graft rejection, and have received immunosuppressants [12]. Purified protein derivative (PPD)-positive before and after transplant and TB-related imaging manifestations (miliary pattern, cavity, punctate apical infiltrates) revealed by chest X-ray are independent risk factors associated with the progression of early onset TB [7].

The mortality of TB patients complicated with liver transplant is high, and the causes of death chiefly cover disseminated TBI and early rejection after transplant [6]. The prognosis of such patients is poor mainly due to complex interactions between anti-TB drugs and immunosuppressants, which cause difficulty in the regulation of the degree of immunosuppression and then lead to severe rejection. In addition, the difficulty in early diagnosis and treatment is also an important reason for the poor prognosis. Studies have summarized that the susceptible population is mostly liver transplant receptors among the SOT cases complicated with TB in recent years (2008–2011), and the mortality is nearly 10% with a significant decrease compared with that in previous years (21%) [13].

2 Diagnosis

Approximately one-third to half of TB patients after liver transplant may have disseminated symptoms or extrapulmonary TB with atypical clinical and imaging manifestations. However, only approximately15% of patients with normal immune systems exhibit the abovementioned manifestations [1]; thus, timely detection or diagnosis of the condition is difficult. Pathogenic detection is the gold standard for the diagnosis of TBI, but using cellular immunological test is still recommended to screen latent TBI (LTBI) in SOT donor–recipients for early treatment.

2.1 LTBI

LTBI is a preclinical stage that is still asymptomatic. Existing diagnostic tests of LTBI are primarily on the basis of the interactions between reactive T-lymphocytes and *M. tuberculosis* antigens. The most commonly used screening methods in clinical practice include tuberculin skin test (TST) and interferon–gamma release assay (IGRA).

2.1.1 TST

TST is used to measure the diameter of induration in a local area 48–72 h after delayed type hypersensitivity is produced by subcutaneously injecting PPDs of tuberculin. Among the general population, the sensibility and specificity of LTBI are better when the diameter of induration is no less than 15 mm. TST detection sensitivity of patients with impaired cellular immunity may be reduced. For organ transplant recipients with active diseases excluded and bacillus Calmette–Guérin (BCG) vaccinated, the diameter of induration no less than 10 mm is considered as positive. However, if the diameter of induration is no less than 5 mm, then a possible presence of LTBI is suggested [14]. TB is likely caused in the TST-positive patients who have been vaccinated for BCG for a long time. Therefore, TST-positive can be used as diagnostic evidence for LTBI in adults. However, patients who are waiting for liver transplant are less sensitive to TST due to skin dysfunctions in patients with end-stage liver disease. Researchers used flow cytometry to detect PPD-specific T-lymphocytes in isolated blood. The results showed that the number of T-lymphocytes in patients who are waiting for liver transplant is the same as that in immune-competent hosts. However, only 50% of patients with PPD-positive in blood are TST-positive before transplant [15]. A retrospective study of 139 patients with active TBI revealed that the preoperative TST-positive rate is only 37% [16]. Therefore, TST is usually used for screening latent TB but is insufficient as a basis for diagnosis.

2.1.2 IGRA

IGRA is an *in vitro* immunoassay for infections with *M. tuberculosis* consisting of QuantiFERON-TB In-Tube (QFT-IT) and T cell spot (T-SPOT) tests. The immunoassay stimulates the secretion of protein-specific immunogens from *M. tuberculosis* and that of γ-interferon from peripheral blood monocytes in TB patients, who are detected by enzyme-linked immunosorbent assay (ELISA) or enzyme-linked immunospot assay (ELISPOT) methods [17, 18]. The specificity and sensibility of TBI detected by IGRA are higher than those of TST, wherein the results are not susceptible to BCG vaccination and most of nonpathogenic mycobacteria [19].

TST and IGRA are highly consistent in the general population. The World Health Organization recommends IGRA for the diagnosis of TBI. Many local and foreign studies have shown that specificity and sensibility of LTBI detected by IGRA in SOT patients are also very high and even higher than those of TST [19]. However, the operating costs of IGRA are higher than those of TST, and the diagnostic value is still controversial in patients with end-stage liver diseases who are receiving immunosuppressants [20]. Researchers have observed 954 TBI patients with normal immune functions up to 4 years, wherein 19 cases eventually developed to active TB, 198 cases were found with positive results at the beginning of IGRA screening, 242 cases had a diameter of induration greater than 10 mm at TST screening, and 604 cases had a diameter of induration greater than 5 mm. Results showed that the 19 cases were positive at the beginning of IGRA screening, but only 10 cases (52.6%) had a diameter of induration greater than 10 mm and 17 cases (89.5%) had a diameter of induration greater than 5 mm at the beginning of TST screening. These findings indicated that IGRA has a higher specificity in the diagnosis of TB progression, but its positive predictive value is not enough to directly identify the dangerous population [21]. In 2014, meta-analysis [22] was performed to evaluate the clinical value of IGRA in the diagnosis of preoperative LTBI in SOT patients with a total of six studies and 751 cases. Results suggested that if their QFT-IT results were positive, then patients cannot be diagnosed with LTBI; and if their QFT-IT results were negative, then the possibility of infection may basically be ruled out. If their T-SPOT results were positive, then patients were less likely to have LTBI; if the results were negative, then the possibility of the infection may basically be ruled out.

In summary, IGRA has a higher sensibility and specificity and greater diagnostic value considering the diagnosis of LTBI. However, existing immunological diagnostic methods including IGRA remain incapable of identifying or diagnosing LTBI. Thus, a full-dress inquiry about such patients is recommended for identifying their medical and TB contact histories to determine related symptoms and signs and provide an overall assessment with a series of auxiliary examinations, such as chest X-ray.

2.2 Active TB

The treatment of active TB after liver transplant is difficult; thus, preoperative diagnosis and treatment is conducted as thoroughly as possible. TB is the most common abortive TB liver transplant [7], wherein the main clinical manifestations include fever, cough, expiratory dyspnea, adenopathy, and atypical manifestations, such as suppurative myositis, skin ulcer, and/or tenosynovitis [2]. Typical symptoms of night sweat and weight loss in TB are uncommon in patients who have undergone liver transplant. Therefore, if a liver transplant patient has a fever of unknown origin, especially if a history or a suspected diagnosis of LTBI exists, then the possibility of TBI should be considered. Even in imaging examinations, classic cavital changes are available in TB patients, except for pulmonary consolidation, miliary pattern, nodules, linear shadows, pleural effusion, and diffused pulmonary interstitial disorders. Bone and joint TB [1] is chiefly manifested as bone destruction, hyperosteogeny, bone sequestration, paravertebral and psoas abscess, and disk failure [23]. Intracranial TB is mainly characterized by meningeal irritation that can cause typical severe headaches, cerebrospinal fluid, cisternal narrowing, and meningeal thickening [24]. Renal TB is commonly manifested with frequent urination, odynuria, urgent urination, hematuresis, turbid urine, lumbago, and whole body poison symptom clinical practice and with hydronephrosis, renal calcification, nephrarctia, and bladder contraction, as revealed by imageological examinations [25]. However, the above abnormalities are rare, atypical, and of limited value in TB diagnosis. Other clinical manifestations also include graft failure and

complications with other pathogenic infections [10], including CMV, community-acquired pneumonia, and infection with nocardiaceae and aspergillus, wherein the combined infection rate is up to 23%. Diagnosis of TB in these types of patients is more difficult [7].

Diagnosis of active TB requires the isolation of *M. tuberculosis*. Neither TST nor IGRA is suitable for the diagnosis of active TB because of the reduced sensitivity of detection in active TB patients and the inability to identify whether the TBI is latent or active. For suspected TB patients, repeated brine stimulation of deep coughing, bronchoalveolar lavage, and lung biopsy are helpful for diagnosis to a certain extent [1, 2]. However, isolating *M. tuberculosis* is more difficult from those sputum specimens extracted from extrapulmonary lesions and can be aided by invasive procedures, such as bronchoscopy, laryngoscopy, tissue biopsy, and bone marrow biopsy [7]. ^{18}F fluorodeoxyglucose (FDG) positron emission tomography/Computed Tomography (PET/CT) imaging can provide diagnostic information for active TB that behaves like malignant tumors [26]. Majority of immunosuppression patients who are clinically suspected with TB are negative by acid-fast staining. However, approximately 50% of patients are positive after repeated testing. The presence of any persistent pathological abnormality, such as granuloma and acid-fast bacillus, is also an indication for anti-TB treatment. Moreover, patients with prolonged fever are always negative in the pathogenic culture and examinations due to atypical imaging manifestations and even non-apparent abnormality. If the patients do not progress after being treated with sensitive antibiotics for more than 2 weeks, such cases should be highly suspected with TB. Where appropriate, patients should be sent for diagnostic anti-TB treatment as soon as possible, and if the treatment is effective within approximately 2–3 weeks, then diagnosis is definitive.

3 Treatment

3.1 Prophylactic chemotherapy regimen

LTBI patients after liver transplant are difficult to diagnose and easier to progress to active TB than the normal population. Therefore, patients with high-risk factors should be vigilant and should undergo prophylactic chemotherapy. The selection of drugs for prophylactic chemotherapy should be based on the drug resistance of local *M. tuberculosis*, recipients' primary diseases, drug toxicity, between-drug interaction, and compliance. The more commonly used treatment regimes include anti-TB treatments with isoniazid for 9 months combined with vitamin B6 for the prevention of nerve injury or rifampicin for 4 months [26]. Our guideline suggests that the preventive treatment regimen should be the same as the local general population [27].

A variety of anti-TB drugs, such as isoniazid, rifampicin, and pyrazinamide, have hepatotoxicity, and the drug combination causes greater liver damage than a single drug, which is extremely unfavorable for patients before and after liver transplant. As reported in a study in Spain in the early years [28], 50% (12) of the 24 TB cases waiting for liver transplant had liver damage in the anti-TB treatment. Therefore, anti-TB treatment should be postponed until after the transplant [9, 29, 30]. However, other researchers have different views and maintained that such patients were safe to undergo anti-TB treatment [29–31]. Singh *et al.* [30]. enrolled 18 LTBI patients waiting for liver transplant (average Child–Pugh scoring: 8 points), wherein liver function test results showed that the treatment with isoniazid for 12 months was not significantly different from that of the untreated control group, and the patients did not need to stop treatment. Similar studies have also shown that receiving anti-TB treatment is safe with isoniazid for 9 months or rifampicin for 4 months [31]. At present, the correct time for anti-TB treatment of patients who have undergone liver transplant is still uncertain. Most researchers believe that anti-TB treatment before the transplant is feasible for compensated cirrhosis patients. However, anti-TB treatment is better to start after the organ transplant [32] for decompensated cirrhosis patients. Moreover, determining whether the liver transplant is safe for those who are already under anti-TB treatment is still unknown.

Liver functions should be closely monitored after the anti-TB treatment begins. Liver functions should be examined once every 2 weeks within the first 6 weeks and once every month after that period of time [29]. If patients have gastrointestinal symptoms and their aspartate transaminase (AST) and/or Alanine transaminase (ALT) levels exceed the upper limit(s) or the AST and/or ALT levels exceed the upper limit(s) five times

even without clinical symptoms, discontinuing the anti-TB drugs is recommended [27]. For patients with severe liver disease who cannot routinely use anti-TB drugs, scholars recommend on the basis of their clinical experience that the combined administration of levofloxacin+ethambutol should be administered for at least 6 months [7, 9]. However, further studies must be conducted on the efficacy of such a treatment.

3.2 Treatment of active TB

Liver toxicity is part of the basic anti-TB drugs, which may interact with immunosuppressants. At present, no consensus is available on treatment regimens for active TB in liver transplant patients. These treatment regimens, as recommended in the guidelines, are mostly derived from certain experiences in the treatment of the population with normal immune functions or immunodeficiency diseases such as HIV, and evidence-based support is lacking for randomized controlled trials. The latest guidelines present that the standard quad-combined anti-TB treatment regimens can be used for adequate regular treatment with the same withdrawal indications as above for patients without clear abnormal liver function abnormalities [27]. Patients with abnormal liver functions should use anti-TB drugs with due care because of hepatotoxicity. Non-hepatotoxic second-line anti-TB drugs, such as streptomycin+ethambutol+quinolones, can be used for treatment with a higher sensitivity but a lower incidence of rejection [33]. At present, a commonly used treatment regimen is isoniazid aminosalicylate and/or rifamycin with the course of treatment lasting for approximately 9–12 months. Second-line anti-TB drugs may be added depending on the specific efficacy. Taking the medication on a daily basis is recommended compared with taking the medication only two to three times a week, making the patient more susceptible to drug resistance [34] and even relapse [35]. Intermittent medication may also cause the concentrations of immunosuppressants to fluctuate greatly, thereby increasing the risk of insufficient immunosuppression.

The course of anti-TB treatment is subject to various factors, such as severity of disease, type of drug, therapeutic response, and bacterial resistance. For patients with local or mild TB lesions, rifamycin should be avoided in the early stages of treatment to reduce the risk of transplant rejection. Evidence suggests that the treatment regimen based on isoniazid aminosalicylate+rifampicin/rifapentine must last for approximately 9–12 months [9] (approximately 18–24 months for scrofula). If the course of treatment is less than 6 months, then recurrence and mortality will increase significantly [33].

A main problem of anti-TB treatment in liver transplant recipients is how to mitigate the effects of drug interactions. Through the interactions between the cytochrome P450 metabolic pathway and calcineurin inhibitor/mTORi, rifampicin may reduce the plasma concentrations of immunosuppressants, such as ciclosporin, tacrolimus, sirolimus, mycophenolate mofetil, and cortisol, thus influencing the efficacy [36]. As recommended in the guidelines, rifampin should be avoided as much as possible in anti-TB treatment combined with SOT [9]. The drug has bee reported in the early years to cause transplant rejection [37]. Recent studies have found a few cases with organ rejection after using rifampicin [38, 39], and neither the incidence of such rejection after transplant nor the mortality of TB is related to whether rifampicin is used as a basic anti-TB drug [12]. No significant difference exists between the two groups of TB patients treated with levofloxacin and rifampicin in the incidence of organ rejection or the mortality of TB, respectively [40]. Rifabutin has anti-TB activity similar to that of rifampicin. However, the rifabutin-induced activity of the cytochrome P450-3A4 enzyme (CYP3A4) is weaker than rifampicin; thus, the concentration of immunosuppressants is maintained better [41]. Whether rifampicin or rifabutin was used, the concentrations of immunosuppressants should be closely monitored, and the doses of immunosuppressants shall be adjusted appropriately.

Recently, the use or combined use of linezolid has shown significant clinical efficacy in anti-TB treatment. Linezolid is an oxazolidinone antibiotic and is safe in the treatment of mild or moderate hepatic insufficiency without affecting the concentrations of immunosuppressants with *in vitro*/*in vivo* activity on *M. tuberculosis*, as found in the drug development phase [42]. However, the efficacy still lacks evidence from large-sample and multi-center random controlled trials. Long-term application of linezolid may cause myelosuppression, gastrointestinal reactions, peripheral neuritis, and other adverse effects, wherein male and elderly patients

are more susceptible [43]. Careful monitoring of hepatic and renal functions, routine blood test, and lactic acid is necessary to avoid serious adverse effects while using linezolid in anti-TB treatment.

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References

[1] Subramanian A.K., Morris M.I., *Mycobacterium tuberculosis* infections in solid organ transplantation, Am. J. Transplant., 2013, 13(Suppl. 4), 68-76.
[2] Tian H., Wang W., Liu H., Zhang X., Early diagnosis and treatment of pulmonary tuberculosis after renal transplant, Chin. J. Health Manage., 2011, 5(6), 345-348.
[3] Lin J., Guo H., Tang Y., Sun W., Xie Z., Zhang L., et al., Clinical characteristics of tuberculosis after renal transplantation and single-center experience in the early diagnosis, J. Clin. Exp. Med., 2013, 12(9), 680-682.
[4] Wang G., Fu B., Zheng X., Li M., Jiang N., Jin H., et al., Diagnosis and treatment of tuberculosis after liver transplant, Chin. J. Hepatic Surg. (Electronic Edition), 2012, 1(2), 113-117.
[5] Doblas A., Alcaide F., Benito N., Tuberculosis in solid organ transplant patients, Enferm. Infect. Microbiol. Clin., 2012, 30(Suppl. 2), 34-39.
[6] Singh N., Paterson D.L., Mycobacterium tuberculosis infection in solid-organ transplant recipients: impact and implications for management, Clin. Infect. Dis., 1998, 27(5), 1266-1277.
[7] Muñoz P., Rodríguez C., Bouza E., Mycobacterium tuberculosis infection in recipients of solid organ transplants, Clin. Infect. Dis., 2005, 40(4), 581-587.
[8] Torre-Cisneros J., Doblas A., Aguado J.M., Tuberculosis after solid-organ transplant: incidence, risk factors, and clinical characteristics in the RESITRA (Spanish Network of Infection in Transplantation) cohort, Clin. Infect. Dis., 2009, 48(12), 1657-1665.
[9] Aguado J.M., Torre-Cisneros J., Fortún J., Benito N., Meije Y., Doblas A., et al., Tuberculosis in solid-organ transplant recipients: consensus statement of the group for the study of infection in transplant recipients (GESITRA) of the Spanish Society of Infectious Diseases and Clinical Microbiology, Clin. Infect. Dis., 2009, 48(9), 1276-1284.
[10] Canet E., Dantal J., Blancho G., Hourmant M., Coupel S., Tuberculosis following kidney transplantation: clinical features and outcome. A French multicentre experience in the last 20 years, Nephrol. Dial. Transplant., 2011, 26(11), 3773-3778.
[11] Clemente W.T., Faria L.C., Lima S.S., Vilela E.G., Lima A.S., Velloso L.F., et al., Tuberculosis in liver transplant recipients: a single Brazilian center experience, Transplantation, 2009, 87(3), 397-401.
[12] Sun H.Y., Munoz P., Torre-Cisneros J., Aguado J.M., Lattes R., Montejo M., et al., Tuberculosis in solid-organ transplant recipients: disease characteristics and outcomes in the current era, Prog. Transplant., 2014, 24(1), 37-43.
[13] Andersen P., Munk M.E., Pollock J.M., Doherty T.M., Specific immune-based diagnosis of tuberculosis, Lancet, 2000, 356(9235), 1099-1104.
[14] Sester U., Junker H., Hodapp T., Schütz A., Thiele B., Meyerhans A., et al., Improved efficiency in detecting cellular immunity towards M. tuberculosis in patients receiving immunosuppressive drug therapy, Nephrol. Dial. Transplant., 2006, 21(11), 3258-3268.
[15] Holty J.E., Gould M.K., Meinke L., Keeffe E.B., Ruoss S.J., Tuberculosis in liver transplant recipients: a systematic review and meta-analysis of individual patient data, Liver Transplant., 2009, 15(8), 894-906.
[16] Pai M., Zwerling A., Menzies D., Systematic review: T -cell-based assays for the diagnosis of latent tuberculosis infection: an update, Ann. Intern. Med., 2008, 149(3), 177-184.
[17] Pai M., Riley L.W., Colford J.M. Jr., Interferon-gamma assays in the immunodiagnosis of tuberculosis: a systematic review, Lancet Infect. Dis., 2004, 4(12), 761-776.
[18] Menzies D., Pai M., Comstock G., Meta-analysis: new tests for the diagnosis of latent tuberculosis infection: areas of uncertainty and recommendations for research, Ann. Intern. Med., 2007, 146(5), 340-354.
[19] Smith R., Cattamanchi A., Steingart K.R., Denkinger C., Dheda K., Winthrop K.L., Interferon-γ release assays for diagnosis of latent tuberculosis infection: evidence in immune-mediated inflammatory disorders, Curr. Opin. Rheumatol., 2011, 23(4), 377-384.
[20] Diel R., Loddenkemper R., Niemann S., Meywald-Walter K., Nienhaus A., Negative and positive predictive value of a whole-blood interferon- γ release assay for developing active tuberculosis: an update, Am. J. Respir. Crit. Care Med., 2011, 183(1), 88-95.
[21] Cao Y., Wang X., Yang B., Cheng X., Meta-analysis on the diagnosis of patients with latent tuberculosis infection before solid organ transplant by *IGRAs*, Evid. Based Med., 2014, 2, 94-98.

[22] Ding E., Tai L., Lu D., Hou S., Feng X., Zhao Y., et al., 18F-FDG PET/CT imaging of one case with multi-organ tuberculosis after liver transplant, Chin. J. Nucl. Med. Mol. Imaging, 2013, 33(6).
[23] Zhao Z., Liang T., Qin Y., Zheng S., Diagnosis and treatment of lumbar tuberculosis after liver transplant, Chin. J. Surg., 2006, 44(9), 630-631.
[24] Yu Z., Investigations on the clinical practice and CT imaging features of 200 cases with intracranial tuberculosis, J. Med. Theory Pract., 2015, 21, 2971-2972.
[25] Xu Z., Xu L., Zhang Q., Zhu J., Ma L., Analysis on the diagnosis and treatment of 155 cases with renal tuberculosis, Infect. Dis. Inf., 2015, 28(2), 105-108.
[26] Bumbacea D., Arend S.M., Eyuboglu F., Fishman J.A., Goletti D., Ison M.G., et al., The risk of tuberculosis in transplant candidates and recipients: a TBNET consensus statement, Eur. Respir. J., 2012, 40(4), 990-1013.
[27] Guidelines for clinical diagnosis and treatment of tuberculosis after organ transplantation in China (2016 Edition), Chin. J. Transplant. (Electronic Version), 2016, 10(2), 49-52.
[28] Aguado J.M., Herrero J.A., Gavalda J., Torre-Cisneros J., Blanes M., Rufí G., et al., Clinical presentation and outcome of tuberculosis in kidney, liver, and heart transplant recipients in Spain, Transplantation, 1997, 63, 1278-1286.
[29] Subramanian A., Dorman S., *Mycobacterium tuberculosis* in solid organ transplant recipients, Am. J. Transplant., 2009, 9(Suppl. 4), S57-S62.
[30] Singh N., Wagener M.M., Gayowski T., Safety and efficacy of isoniazid chemoprophylaxis administered during liver transplant candidacy for the prevention of posttransplant tuberculosis, Transplantation, 2002, 74(6), 892-895.
[31] Jahng A.W., Tran T., Bui L., Joyner J.L., Safety of treatment of latent tuberculosis infection in compensated cirrhotic patients during transplant candidacy period, Transplantation, 2007, 83(12), 1557-1562.
[32] Yehia B.R., Blumberg E.A., Mycobacterium tuberculosis infection in liver transplantation, Liver Transplant., 2010, 16(10), 1129-1135.
[33] Barcena R., Oton E., Angeles Moreno M, Fortún J., Garcia-Gonzalez M., Moreno A., et al., Is liver transplantation advisable for isoniazid fulminant hepatitis in active extrapulmonary tuberculosis? Am. J. Transplant., 2005, 5(11), 2796-2798.
[34] Menzies D., Benedetti A., Paydar A., Martin I., Royce S., Pai M., et al., Effect of duration and intermittency of rifampin on tuberculosis treatment outcomes: a systematic review and meta-analysis, PLoS Med., 2009, 6(9), 188-188.
[35] Chang K.C., Leung C.C., Yew W.W., Chan S.L., Tam C.M., Dosing schedules of 6-month regimens and relapse for pulmonary tuberculosis, Am. J. Respir. Crit. Care Med., 2006, 174(10), 1153-1158.
[36] Márquez M., Fernández-Gutiérrez C., Montes-de-Oca M., Blanco M.J., Brun F., Rodríguez-Ramos C., et al., Chronic antigenic stimuli as a possible explanation for the immunodepression caused by liver cirrhosis, Clin. Exp. Immunol., 2009, 158(2), 219-229.
[37] Bhaloo S., Prasad G.V., Severe reduction in tacrolimus levels with rifampin despite multiple cytochrome P450 inhibitors: a case report, Transplant. Proc., 2003, 35(7), 2449-2451.
[38] Hsu M.S., Wang J.L., Ko W.J., Lee P.H., Chou N.K., Wang S.S., et al., Clinical features and outcome of tuberculosis in solid organ transplant recipients, Am. J. Med. Sci., 2007, 334(2), 106-110.
[39] Chou N.K., Wang J.L., Chi N.H., Wu I.H., Huang S.C., Chen Y.S., et al., Tuberculosis after heart transplantation: twenty years of experience in a single center in Taiwan, Transplant. Proc., 2008, 40(8), 2631-2633.
[40] Ha Y.E., Joo E.J., Park S.Y., Wi Y.M., Kang C.I., Chung D.R., et al., Tacrolimus as a risk factor for tuberculosis and outcome of treatment with rifampicin in solid organ transplant recipients, Transplant. Infect. Dis., 2012, 14(6), 626-634.
[41] Hickey M.D., Quan D.J., ChinHong P.V., Roberts J.P., Use of rifabutin for the treatment of a latent tuberculosis infection in a patient after solid organ transplantation, Liver Transplant., 2013, 19(4), 457-461.
[42] Cynamon M.H., Klemens S.P., Sharpe C.A., Chase S., Activities of several novel oxazolidinones against *Mycobacterium tuberculosis* in a murine model, Antimicrob. Agents Chemother., 1999, 43(5), 1189-1191.
[43] Anger H.A., Dworkin F., Sharma S., Munsiff S.S., Nilsen D.M., Ahuja S.D., Linezolid use for treatment of multidrug-resistant and extensively drug-resistant tuberculosis, J. Antimicrob. Chemother., 2010, 65(4), 775-783.