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**Fluoroquinolones for the treatment of latent *Mycobacterium tuberculosis* infection in liver transplantation**

Silva JT *et al*. Fluoroquinolones for latent tuberculosis infection in liver transplantation

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**Abstract**

Solid organ transplantation (SOT) is the best treatment option for end-stage organ disease. Newer immunosuppressive agents have reduced the incidence of graft rejection but have increased the risk of infection, particularly due to the reactivation of latent infections due to opportunistic agents such as *Mycobacterium tuberculosis*. Active tuberculosis (TB) after SOT is a significant cause of morbidity and mortality. Most cases of posttransplant TB are secondary to reactivation of latent tuberculosis infection (LTBI) due to the effects of long-term immunosuppressive therapy. Risk minimization strategies have been developed to diagnose LTBI and initiate treatment prior to transplantation. Isoniazid with vitamin B6 supplementation is the treatment of choice. However, liver transplantation (LT) candidates and recipients have an increased risk of isoniazid-induced liver toxicity, leading to lower treatment completion rates than in other SOT populations. Fluoroquinolones (FQs) exhibit good *in vitro* antimycobacterial activity and a lower risk of drug-induced liver injury than isoniazid. In the present review, we highlight the disease burden posed by posttransplant TB and summarize the emerging clinical evidence supporting the use of FQs for the treatment of LTBI in LT recipients and candidates.

**Key words:** Fluoroquinolones; *Mycobacterium tuberculosis*; Latent tuberculosis infection; Liver transplantation; Drug-induced liver graft injury

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**Core tip:** Active tuberculosis after solid organ transplantation, particularly after liver transplantation, has a dismal outcome. This review focuses on the burden of active tuberculosis after liver transplantation and summarizes the most recent data concerning the use of isoniazid for the treatment of latent tuberculosis infection in liver transplant recipients and candidates. In addition, we review the most relevant clinical experience in the use of fluoroquinolones as an alternative approach with a favorable safety profile for the treatment of latent tuberculosis infection in the liver transplant setting.

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**INTRODUCTION**

Solid organ transplantation (SOT) is the best treatment option for end-stage organ disease. New immunosuppressive agents have reduced the incidence of acute graft rejection but have increased the risk of infection and the development of *de novo* malignancies in the long term[1-4]. Prophylactic and preemptive treatment strategies have been especially effective in diminishing the incidence of donor and recipient-derived infections as well as the frequency of most opportunistic infections (OI) in the first six months after transplantation. However, the incidence of active tuberculosis (TB), one of the most concerning OIs after SOT, is still significant. A study that prospectively analyzed the online database of the Spanish Network of Infection in Transplantation (RESITRA) found that *Mycobacterium tuberculosis* (*M. tuberculosis*) was responsible for almost a quarter of the cases of OI diagnosed after the sixth month posttransplantation[5]. Cases of disseminated TB were not infrequent.

In this review, we focus on the importance of TB after liver transplantation (LT). We also discuss the most important strategies for the prevention of *M. tuberculosis* reactivation in LT recipients, particularly the role that fluoroquinolones (FQs) could play in the treatment of latent tuberculosis infection (LTBI) in LT candidates and recipients.

**THE BURDEN OF *M. TUBERCULOSIS* AFTER LT**

Active TB poses important challenges to clinicians who attend SOT recipients[6], with an incidence that can vary significantly-from 0.35% to 15%-depending on the prevalence of TB in a specific region or country and the type of SOT performed. A prospective study that included 16 transplant centers of the Spanish Network for Research in Infectious Diseases (REIPI) reported that LT recipients were at particular risk and had the third highest incidence rate, with 541 cases per 100000 transplant recipients per year, much higher than the rates in recipients of similar SOTs, such as kidney transplant (KT) and heart transplant (HT) recipients, which were 358 and 255/100000 patients per year, respectively[7].

Pulmonary TB (PTB) is the most frequently presenting type of *M. tuberculosis* infection after LT[8,9]. The risk for extrapulmonary (EPTB) or disseminated TB (DTB) is also higher than that observed in the general population; these conditions have an incidence rate of up to 33% among all patients[10, 11]. In these cases, patients tend to complain only of fever or unspecific constitutional symptoms, without any other accompanying signs[6,12]; thus, clinicians should always consider this disease and have a high index of suspicion for active TB[13]. Active TB treatment after LT is also problematic. The incidence of isoniazid-induced hepatotoxicity after LT is increased when isoniazid is combined with rifampicin[14], and accordant histological changes can be found in up to 83% of treated LT recipients[15]. Interactions with immunosuppressive drugs can also favor allograft rejection; rifampicin, a potent inducer of the cytochrome P450 enzyme system, can reduce the blood levels of most immunosuppressants used in daily practice[15,16].

A number of studies have exhaustively addressed active TB in the LT setting. Abad *et al*[17], who reviewed 187 MEDLINE, EMBASE, and OVID publications, thoroughly described a total of 2082 cases of TB in SOT recipients, including 253 cases after LT. In this specific population, the relative frequency and median interval from transplantation to presentation of PTB, EPTB and DTB were 36.51%, 36.51% and 26.91% and 4, 9, and 48 mo, respectively. The liver allograft was involved in 30.0% of recipients in whom *M. tuberculosis* was isolated outside the pulmonary system, and 3.51% experienced allograft dysfunction or loss. Notably, 27.5% of LT recipients developed anti-TB drug-induced hepatoxicity, which was a higher percentage than in the overall cohort (19.56%). A systematic review and meta-analysis of TB after LT identified 139 cases of active TB. Most patients were diagnosed with EPTB (67%), and in 26, there was allograft involvement[18]. TB drug therapy was stopped or changed in 35% of the patients, mostly due to hepatoxicity (80%)[18]. Póvoas *et al*[19] described 8 cases of active TB after LT diagnosed in a transplant unit located in Lisbon, Portugal, over a five-year span. The incidence rates of PTB, EPTB and DTB were 37.5%, 37.5% and 25.0%, respectively. Liver allograft involvement was identified in 1 patient. Most cases were diagnosed more than 12 mo after transplantation. All patients received a four-drug treatment regimen, and one patient developed mild to moderate cholestasis that did not require therapy discontinuation[19].

The mortality rate of TB after LT can be as high as 50%, 20.31%, and 37.5%, respectively of the published studies[9,17,19].

TB can be secondary to reactivation of a latent infection or due to a new infection after transplantation, which can be acquired in the community or the healthcare environment or can be donor-derived[12,17]. However, the most common way of developing active TB disease after LT is by reactivation of a latent infection upon the initiation of immunosuppressive therapy[17]. For this reason, in recent years, an important effort has been made to diagnose and treat LTBI in all SOT candidates, including LT candidates.

**TREATMENT OF LTBI IN LT**

LTBI can be defined as an infection by viable *M. tuberculosis* microorganisms that are resting in a dormant state[20]. The LT candidate or recipient must have no signs, symptoms or radiographic findings of active TB disease[20].

Although a discussion concerning the controversies about the best method of diagnosing LTBI is beyond the scope of this article, all LT candidates should be screened for LTBI (Table 1). Screening requires collection of an exhaustive clinical history, a careful physical examination, a tuberculin skin test (TST) and/or tuberculosis interferon-γ release assay (IGRA), and a chest radiograph[21]. Isoniazid (2.5 to 5 mg/kg per day, without exceeding 300 mg/day) plus vitamin B6 (25 to 50 mg/day) for 9 mo is the traditional treatment of choice for LTBI in the SOT population[20,22,23] (Table 1). Treatment should ideally be started before LT, although in candidates with advanced end-stage liver disease, current clinical guidelines recommend different LTBI treatments until liver function is stable after LT[22,23]. Another alternative to isoniazid is rifampicin for 4 months, although such a regimen should be restricted to the pretransplant period due to the risk of drug interactions with immunosuppressive agents. Combination treatment with isoniazid/rifampicin for 3 to 4 months carries an important cumulative risk of fulminant hepatitis and should not be prescribed to patients with liver disease[22]. Two recent studies describing the experience with a 12-wk course of once-weekly directly observed therapy (DOT) with isoniazid plus rifapentine included 8 and 7 LT candidates[24,25] and reported adequate tolerance and a relatively high completion rate. However, data are still scarce, and future multicenter prospective studies are warranted to confirm the safety of this treatment regimen and to identify the most suitable LT candidates.

Thus, LTBI treatment in LT candidates or recipients is especially difficult. Isoniazid is usually poorly tolerated, and it has been suggested that drug-induced hepatitis can occur in up to 6%-20% of LT recipients[26]. In the RESITRA study, only 29.6% of LT patients with a TST positivity actually received treatment, a rate substantially lower than that observed in the overall cohort of SOT recipients (mean of 43.5%)[7]. A recent European survey performed in 55 transplant programs from 19 countries reported that the rate of LTBI treatment prescription was significantly lower for LT candidates than for other SOT candidates (38% *vs* 73%, respectively)[27]. A retrospective Canadian study that compared the tolerability of LTBI treatment in 23 LT candidates and 24 LT recipients against 130 non-liver SOT candidates plus 23 non-LT SOT recipients concluded that the completion rate of LTBI therapy with isoniazid and/or rifampicin was significantly lower in LT candidates or recipients than in non-LT candidates and recipients [36.1% *vs* 73.9%, respectively; odds ratio (OR) = 0.20; *P* < 0.001][28]. Therapy discontinuation due to liver enzyme elevation was also more frequent in LT candidates and recipients than in non-LT candidates and recipients (28.3% *vs* 3.5%; OR = 10.48; *P* value < 0.001)[28]. A study that included 15 LT recipients diagnosed with LTBI and treated with 300 mg of daily isoniazid plus 50 mg of pyridoxine for six months reported that 53% of patients required premature discontinuation of the therapy[29]. The most important side effects were thrombocytopenia, hepatotoxicity, rejection, and tacrolimus toxicity. All patients had started LTBI treatment within the first six months after transplantation. A similar South Korean study reported that the incidence rate of isoniazid-induced hepatotoxicity was significantly lower in LT recipients with an aspartate aminotransferase (AST) level lower than 50 than in those with an AST level higher than 50[30]. The authors of both studies suggested deferring LTBI treatment until liver allograft function was stable, avoiding its prescription in the early post-LT period[29,30]. However, this delay could lead to an increased risk of TB reactivation, as most cases of active TB are diagnosed within the first months after transplantation[6,8,12]. Moreover, in candidates already receiving isoniazid-based LTBI treatment regimen, therapy must be stopped at the time of LT and resumed only when the allograft is stabilized[22], delaying the end of treatment.

**EXPERIENCE WITH FQs FOR THE TREATMENT OF LTBI IN LT**

Most data for LTBI treated with FQ-based regimens are derived from preventive therapy of multidrug resistant TB cases. Levofloxacin and moxifloxacin have been shown to exhibit good *in vitro* activity against TB[31,32]. In addition, in these series, levofloxacin and moxifloxacin appeared to be well tolerated and cost-effective[33,34], with treatment completion rates as high as 83% and 100%[35]. FQs, such as levofloxacin, also have a lower hepatotoxic potential than other anti-TB drugs[36]. However, it must be remembered that serious side effects are associated with FQs, such as QT interval prolongation[37], tenosynovitis[38] and an increased risk of aortic aneurysm and dissection[39], which is a theoretical concern in long-term therapeutic regimens. Data regarding the risk of rhegmatogenous retinal detachment are still under debate due to contradictions in the published data[40,41]. Furthermore, the European Medicines Agency (EMA) recently issued a warning regarding the risk of hepatotoxicity associated with moxifloxacin, recommending close follow-up during treatment.

In the LT setting, FQs have been used particularly as part of isoniazid- or rifampin-sparing regimens prescribed to recipients diagnosed with active TB. Lee *et al*[42] described nine LT recipients diagnosed with active TB and treated with a therapeutic regimen that principally included ethambutol, cycloserine and a FQ (levofloxacin in 6, moxifloxacin in 1 and ofloxacin in 2 recipients). All nine patients successfully completed treatment and did not experience any apparent FQ-associated side effects. Several case reports of LT recipients treated with a therapeutic regimen that included levofloxacin[43,44] or moxifloxacin[45] have also been published. FQs were administered for periods ranging from 2 mo to 18 mo. No cases of FQ-induced adverse effects were reported.

Regrettably, data concerning the use of FQs in LT for LTBI treatment are still scarce and mostly based on retrospective single-center studies with a small series of patients (Table 2). To date, only one prospective multicenter randomized study has compared the efﬁcacy and safety of levoﬂoxacin (500 mg daily for 9 mo) initiated before transplantation to isoniazid (300 mg every day for 9 mo) initiated between 3 and 6 months after transplantation[46]. Isoniazid was started only when liver function was considered stable, *i.e.*, when the transaminase, alkaline phosphatase, and bilirubin levels did not exceed twice the upper limit of normal. The primary efﬁcacy endpoint was the number of patients who developed tuberculosis at 18 mo after transplantation, whereas the secondary aim was to determine whether adverse events limited the efﬁcacy of levoﬂoxacin. The study was active between January 2012 and February 2014, when a safety analysis resulted in suspension of the trial. Notably, 6 of the 33 candidates (18.2%) in the levofloxacin arm developed tenosynovitis, which required stopping the drug, and 6.1% were diagnosed with severe hepatotoxicity, which resolved after discontinuing the antibiotic. Tenosynovitis occurred from 14 to 133 days after the start of prophylaxis. The authors concluded that levofloxacin was associated with an unacceptably high incidence of tenosynovitis in LT candidates. However, it should be mentioned that only 18 of the 31 LT recipients in the isoniazid arm (58.1%) actually began prophylaxis, and only 10 (32.2%) completed the 9-month treatment course[46]. Hepatotoxicity, which was observed in 38.9% of patients receiving isoniazid, was the most common adverse event associated with this drug. No cases of TB were diagnosed during follow-up.

Since the publication of the RESITRA cohort study, several small single-center reports have been published (Table 2). Tien *et al*[47] described an experience with 44 LT candidates treated for LTBI, including 25 patients who received FQ (17, levoﬂoxacin; and 8, moxiﬂoxacin). Adverse events were described in 14 of the 25 (56%) treated patients, including 4 (16%) with musculoskeletal symptoms that ranged from diffuse joint pain to unilateral tendinopathy. One patient required permanent FQ discontinuation, whereas the remaining 3 patients were able to complete the 9-mo treatment after temporary suspension of the drug. The incidence of adverse events leading to permanent discontinuation significantly differed among the drugs: from 8% for FQ to 33% and 40% for rifampicin and isoniazid, respectively[47]. The same authors also described 6 LT recipients who received FQs after transplantation for LTBI. Although one recipient presented joint pain, he was able to complete treatment. No cases of FQ-induced hepatotoxicity prior to or after transplantation were reported, and none of these patients developed TB during follow-up[47]. Grim *et al*[48] published a retrospective study that focused on the tolerability and completion of LTBI treatment in SOT candidates. Of the 129 patients included, 30 were LT and 8 were LT/kidney transplant candidates, and 8 (21.0%) received moxifloxacin. Although much data are lacking, in this particular group, there were no early discontinuations of the drug, and at least 2 patients (25.0%) completed treatment (data for the other 6 candidates concerning the end of treatment was not retrieved). Sgarabotto *et al*[49] reported an experience with 35 LT recipients who received a combination course of levofloxacin and ethambutol from posttransplant day 1 until hospital discharge and three times weekly for 1 year thereafter. Four patients (11.4%) developed side events that required treatment cessation. Interestingly, during follow-up, TB was diagnosed in 2 patients (5.7%); one had discontinued LTBI treatment due to drug-induced side effects[49]. Anecdotally, a combination of levofloxacin and pyrazinamide for MDR TB prophylaxis prescribed to 57 SOT recipients, including 3 LT patients, resulted in a high incidence of side effects (approximately 1.4 events/patient) with very limited tolerability[50].

**CONCLUSION**

Active TB is a serious OI after SOT, particularly after LT. Treatment is difficult due to the increased risk of drug-induced liver allograft injury, fulminant hepatic failure and rejection. Most centers either do not prescribe or delay the start of LTBI treatment, as it seems reasonable to consider therapy with isoniazid only in patients with compensated cirrhosis or good liver allograft function and in whom hepatotoxicity can be closely monitored. FQs, which have good anti-TB activity and appear to be less hepatotoxic than isoniazid, could be an alternative for LTBI treatment in the LT setting. Data in some points are small and conflicting, with the rate of permanent withdrawal of the FQ due to side effects ranging from 6% to 33% of all treated patients. More studies are necessary to determine which patients could have the greatest benefit from this therapeutic regimen as well as to compare the tolerability and side effects of levofloxacin *vs* moxifloxacin and the risk of multidrug-resistant gram-negative bacterial selection. These studies would also allow us to determine the real efficacy of FQs in preventing LTBI in the LT setting.

**REFERENCES**

1 **Fishman JA**, Issa NC. Infection in organ transplantation: risk factors and evolving patterns of infection. *Infect Dis Clin North Am* 2010; **24**: 273-283 [PMID: 20466270 DOI: 10.1016/j.idc.2010.01.005]

2 **Fishman JA**. Infections in immunocompromised hosts and organ transplant recipients: essentials. *Liver Transpl* 2011; **17** Suppl 3: S34-S37 [PMID: 21748845 DOI: 10.1002/lt.22378]

3 **Fishman JA**. Opportunistic infections--coming to the limits of immunosuppression? *Cold Spring Harb Perspect Med* 2013; **3**: a015669 [PMID: 24086067 DOI: 10.1101/cshperspect.a015669]

4 **Fishman JA**. Infection in solid-organ transplant recipients. *N Engl J Med* 2007; **357**: 2601-2614 [PMID: 18094380 DOI: 10.1056/NEJMra064928]

5 **Garrido RS**, Aguado JM, Díaz-Pedroche C, Len O, Montejo M, Moreno A, Gurguí M, Torre-Cisneros J, Pareja F, Segovia J, Garcia M, Lumbreras C. A review of critical periods for opportunistic infection in the new transplantation era. *Transplantation* 2006; **82**: 1457-1462 [PMID: 17164717 DOI: 10.1097/01.tp.0000245676.43979.86]

6 **Aguado JM**, Silva JT, Samanta P, Singh N. Tuberculosis and Transplantation. *Microbiol Spectr* 2016; **4** [PMID: 27809952 DOI: 10.1128/microbiolspec.TNMI7-0005-2016]

7 **Torre-Cisneros J**, Doblas A, Aguado JM, San Juan R, Blanes M, Montejo M, Cervera C, Len O, Carratala J, Cisneros JM, Bou G, Muñoz P, Ramos A, Gurgui M, Borrell N, Fortún J, Moreno A, Gavalda J; Spanish Network for Research in Infectious Diseases. 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**: 1657-1665 [PMID: 19445585 DOI: 10.1086/599035]

8 **Yehia BR**, Blumberg EA. Mycobacterium tuberculosis infection in liver transplantation. *Liver Transpl* 2010; **16**: 1129-1135 [PMID: 20879011 DOI: 10.1002/lt.22133]

9 **Aguado JM**, Herrero JA, Gavaldá J, Torre-Cisneros J, Blanes M, Rufí G, Moreno A, Gurguí M, Hayek M, Lumbreras C, Cantarell C. Clinical presentation and outcome of tuberculosis in kidney, liver, and heart transplant recipients in Spain. Spanish Transplantation Infection Study Group, GESITRA. *Transplantation* 1997; **63**: 1278-1286 [PMID: 9158022]

10 **Singh N**, Paterson DL. Mycobacterium tuberculosis infection in solid-organ transplant recipients: impact and implications for management. *Clin Infect Dis* 1998; **27**: 1266-1277 [PMID: 9827281 DOI: 10.1086/514993]

11 **Muñoz P**, Rodríguez C, Bouza E. Mycobacterium tuberculosis infection in recipients of solid organ transplants. *Clin Infect Dis* 2005; **40**: 581-587 [PMID: 15712081 DOI: 10.1086/427692]

12 **Demir E**, Sever MS. Posttransplant Tuberculosis. *Exp Clin Transplant* 2017; **15**: 10-15 [PMID: 28260424 DOI: 10.6002/ect.mesot2016.L32]

13 **Wang B**, Lü Y, Yú L, Liu C, Wu Z, Pan C. Diagnosis and treatment for tuberculosis infection in liver transplant recipients: case reports. *Transplant Proc* 2007; **39**: 3509-3511 [PMID: 18089423 DOI: 10.1016/j.transproceed.2007.08.093]

14 **Schluger LK**, Sheiner PA, Jonas M, Guarrera JV, Fiel IM, Meyers B, Berk PD. Isoniazid hepatotoxicity after orthotopic liver transplantation. *Mt Sinai J Med* 1996; **63**: 364-369 [PMID: 8898542]

15 **Meyers BR**, Papanicolaou GA, Sheiner P, Emre S, Miller C. Tuberculosis in orthotopic liver transplant patients: increased toxicity of recommended agents; cure of disseminated infection with nonconventional regimens. *Transplantation* 2000; **69**: 64-69 [PMID: 10653382]

16 **Kumar N**, Kedarisetty CK, Kumar S, Khillan V, Sarin SK. Antitubercular therapy in patients with cirrhosis: challenges and options. *World J Gastroenterol* 2014; **20**: 5760-5772 [PMID: 24914337 DOI: 10.3748/wjg.v20.i19.5760]

17 **Abad CLR**, Razonable RR. Mycobacterium tuberculosis after solid organ transplantation: A review of more than 2000 cases. *Clin Transplant* 2018; **32**: e13259 [PMID: 29656530 DOI: 10.1111/ctr.13259]

18 **Holty JE**, Gould MK, Meinke L, Keeffe EB, Ruoss SJ. Tuberculosis in liver transplant recipients: a systematic review and meta-analysis of individual patient data. *Liver Transpl* 2009; **15**: 894-906 [PMID: 19642133 DOI: 10.1002/lt.21709]

19 **Póvoas D**, Machado J, Perdigoto R, Morbey A, Veloso J, Glória H, Mateus É, Martins A, Maltez F, Barroso E. Tuberculosis in Liver Transplant Recipients: A Report of Eight Cases During a Five Year Period. *Acta Med Port* 2017; **30**: 41-46 [PMID: 28501036]

20 **Meije Y**, Piersimoni C, Torre-Cisneros J, Dilektasli AG, Aguado JM; ESCMID Study Group of Infection in Compromised Hosts. Mycobacterial infections in solid organ transplant recipients. *Clin Microbiol Infect* 2014; **20** Suppl 7: 89-101 [PMID: 24707957 DOI: 10.1111/1469-0691.12641]

21 **Epstein DJ**, Subramanian AK. Prevention and Management of Tuberculosis in Solid Organ Transplant Recipients. *Infect Dis Clin North Am* 2018; **32**: 703-718 [PMID: 30146031 DOI: 10.1016/j.idc.2018.05.002]

22 **Bosch A**, Valour F, Dumitrescu O, Dumortier J, Radenne S, Pages-Ecochard M, Chidiac C, Ferry T, Perpoint T, Miailhes P, Conrad A, Goutelle S, Ader F; Lyon TB study Group. A practical approach to tuberculosis diagnosis and treatment in liver transplant recipients in a low-prevalence area. *Med Mal Infect* 2019; **49**: 231-240 [PMID: 30591271 DOI: 10.1016/j.medmal.2018.11.013]

23 **Santoro-Lopes G**, Subramanian AK, Molina I, Aguado JM, Rabagliatti R, Len O. Tuberculosis Recommendations for Solid Organ Transplant Recipients and Donors. *Transplantation* 2018; **102**: S60-S65 [PMID: 29381579 DOI: 10.1097/TP.0000000000002014]

24 **Knoll BM**, Nog R, Wu Y, Dhand A. Three months of weekly rifapentine plus isoniazid for latent tuberculosis treatment in solid organ transplant candidates. *Infection* 2017; **45**: 335-339 [PMID: 28276008 DOI: 10.1007/s15010-017-1004-5]

25 **de Castilla DL**, Rakita RM, Spitters CE, Narita M, Jain R, Limaye AP. Short-course isoniazid plus rifapentine directly observed therapy for latent tuberculosis in solid-organ transplant candidates. *Transplantation* 2014; **97**: 206-211 [PMID: 24142036 DOI: 10.1097/TP.0b013e3182a94a2f]

26 **Rajagopala S**, Olithselvan A, Varghese J, Shanmugam N, Rela M. Latent Mycobacterium tuberculosis Infection in Liver Transplant Recipients-Controversies in Current Diagnosis and Management. *J Clin Exp Hepatol* 2011; **1**: 34-37 [PMID: 25755308 DOI: 10.1016/S0973-6883(11)60120-5]

27 **Boillat-Blanco N**, Aguado JM, Aubert JD, Sester M, Grossi P, Kamar N, Pascual M, Manuel O; ESCMID Study Group of Infection in Compromised Hosts. European survey on the management of tuberculosis in solid-organ transplant recipients and candidates. *Transpl Int* 2013; **26**: e69-e70 [PMID: 23582103 DOI: 10.1111/tri.12102]

28 **Sidhu A**, Verma G, Humar A, Kumar D. Outcome of latent tuberculosis infection in solid organ transplant recipients over a 10-year period. *Transplantation* 2014; **98**: 671-675 [PMID: 24825525 DOI: 10.1097/TP.0000000000000133]

29 **Jafri SM**, Singal AG, Kaul D, Fontana RJ. Detection and management of latent tuberculosis in liver transplant patients. *Liver Transpl* 2011; **17**: 306-314 [PMID: 21384513 DOI: 10.1002/lt.22203]

30 **Moon HH**, Park SY, Kim JM, Park JB, Kwon CHD, Peck KR, Kim SJ, Lee SK, Joh JW. Isoniazid Prophylaxis for Latent Tuberculosis Infections in Liver Transplant Recipients in a Tuberculosis-Endemic Area. *Ann Transplant* 2017; **22**: 338-345 [PMID: 28579606 DOI: 10.12659/AOT.902989]

31 **Cremades R**, Rodríguez JC, García-Pachón E, Galiana A, Ruiz-García M, López P, Royo G. Comparison of the bactericidal activity of various fluoroquinolones against Mycobacterium tuberculosis in an in vitro experimental model. *J Antimicrob Chemother* 2011; **66**: 2281-2283 [PMID: 21733966 DOI: 10.1093/jac/dkr281]

32 **García-Tapia A**, Rodríguez JC, Ruiz M, Royo G. Action of fluoroquinolones and Linezolid on logarithmic- and stationary-phase culture of Mycobacterium tuberculosis. *Chemotherapy* 2004; **50**: 211-213 [PMID: 15523179 DOI: 10.1159/000081707]

33 **Holland DP**, Sanders GD, Hamilton CD, Stout JE. Strategies for treating latent multiple-drug resistant tuberculosis: a decision analysis. *PLoS One* 2012; **7**: e30194 [PMID: 22272302 DOI: 10.1371/journal.pone.0030194]

34 **Seddon JA**, Garcia-Prats AJ, Kampmann B, Schaaf HS, Hesseling AC. Toxicity and tolerability of fluoroquinolone-based preventive therapy for childhood contacts of multidrug-resistant tuberculosis. *Pediatr Infect Dis J* 2014; **33**: 1098-1099 [PMID: 25361192 DOI: 10.1097/INF.0000000000000369]

35 **Bamrah S**, Brostrom R, Dorina F, Setik L, Song R, Kawamura LM, Heetderks A, Mase S. Treatment for LTBI in contacts of MDR-TB patients, Federated States of Micronesia, 2009-2012. *Int J Tuberc Lung Dis* 2014; **18**: 912-918 [PMID: 25199004 DOI: 10.5588/ijtld.13.0028]

36 **Yew WW**, Leung CC. Antituberculosis drugs and hepatotoxicity. *Respirology* 2006; **11**: 699-707 [PMID: 17052297 DOI: 10.1111/j.1440-1843.2006.00941.x]

37 **Khan F**, Ismail M, Khan Q, Ali Z. Moxifloxacin-induced QT interval prolongation and torsades de pointes: a narrative review. *Expert Opin Drug Saf* 2018; **17**: 1029-1039 [PMID: 30193085 DOI: 10.1080/14740338.2018.1520837]

38 **Bolon B**. Mini-Review: Toxic Tendinopathy. *Toxicol Pathol* 2017; **45**: 834-837 [PMID: 28553748 DOI: 10.1177/0192623317711614]

39 **Noman AT**, Qazi AH, Alqasrawi M, Ayinde H, Tleyjeh IM, Lindower P, Bin Abdulhak AA. Fluoroquinolones and the risk of aortopathy: A systematic review and meta-analysis. *Int J Cardiol* 2019; **274**: 299-302 [PMID: 30309682 DOI: 10.1016/j.ijcard.2018.09.067]

40 **Raguideau F**, Lemaitre M, Dray-Spira R, Zureik M. Association Between Oral Fluoroquinolone Use and Retinal Detachment. *JAMA Ophthalmol* 2016; **134**: 415-421 [PMID: 26967005 DOI: 10.1001/jamaophthalmol.2015.6205]

41 **Alves C**, Penedones A, Mendes D, Batel Marques F. A systematic review and meta-analysis of the association between systemic fluoroquinolones and retinal detachment. *Acta Ophthalmol* 2016; **94**: e251-e259 [PMID: 26846201 DOI: 10.1111/aos.12931]

42 **Lee YT**, Hwang S, Lee SG, Kim KW, Choi NK, Park GC, Yu YD, Yoo JW, Kim WS, Shim TS. Living-donor liver transplantation in patients with concurrent active tuberculosis at transplantation. *Int J Tuberc Lung Dis* 2010; **14**: 1039-1044 [PMID: 20626950]

43 **Jung BH**, Park JI, Lee SG. Urgent Living-Donor Liver Transplantation in a Patient With Concurrent Active Tuberculosis: A Case Report. *Transplant Proc* 2018; **50**: 910-914 [PMID: 29661461 DOI: 10.1016/j.transproceed.2018.02.013]

44 **Codeluppi M**, Cocchi S, Guaraldi G, Di Benedetto F, De Ruvo N, Meacci M, Meccugni B, Esposito R, Gerunda GE. Posttransplant Mycobacterium tuberculosis disease following liver transplantation and the need for cautious evaluation of Quantiferon TB GOLD results in the transplant setting: a case report. *Transplant Proc* 2006; **38**: 1083-1085 [PMID: 16757271 DOI: 10.1016/j.transproceed.2006.02.012]

45 **Rodríguez-Framil M**, Antela A, Prieto A, Otero E, Molina E, Varo E. Tuberculous hepatic abscess appearing after liver transplantation in a patient with human immunodeficiency virus and hepatitis B and C virus co-infection. *Transpl Infect Dis* 2011; **13**: 515-519 [PMID: 21395955 DOI: 10.1111/j.1399-3062.2011.00620.x]

46 **Torre-Cisneros J**, San-Juan R, Rosso-Fernández CM, Silva JT, Muñoz-Sanz A, Muñoz P, Miguez E, Martín-Dávila P, López-Ruz MA, Vidal E, Cordero E, Montejo M, Blanes M, Fariñas MC, Herrero JI, Rodrigo J, Aguado JM. Tuberculosis prophylaxis with levofloxacin in liver transplant patients is associated with a high incidence of tenosynovitis: safety analysis of a multicenter randomized trial. *Clin Infect Dis* 2015; **60**: 1642-1649 [PMID: 25722196 DOI: 10.1093/cid/civ156]

47 **Tien V**, Robilotti E, Callister D, Subramanian A, Lutchman G, Ho DY. Tolerability of Fluoroquinolones in Management of Latent Tuberculosis in Liver Transplant Candidates. *Clin Infect Dis* 2015; **61**: 1631-1632 [PMID: 26224000 DOI: 10.1093/cid/civ639]

48 **Grim SA**, Layden JE, Roth P, Gallitano S, Adams W, Clark NM. Latent tuberculosis in kidney and liver transplant patients: a review of treatment practices and outcomes. *Transpl Infect Dis* 2015; **17**: 768-777 [PMID: 26263530 DOI: 10.1111/tid.12436]

49 **Sgarabotto D**, Fasolato S, Vianello F, Vittadello F, Boccagni P, Ferrarese A, Burra P, Angeli P, Cillo U. Antibiotic prophylaxis for preventing postorthotopic liver transplant tuberculosis: is there a safe alternative to isoniazid? *Transpl Int* 2017; **30**: 734-736 [PMID: 28332726 DOI: 10.1111/tri.12955]

50 **Lou HX**, Shullo MA, McKaveney TP. Limited tolerability of levofloxacin and pyrazinamide for multidrug-resistant tuberculosis prophylaxis in a solid organ transplant population. *Pharmacotherapy* 2002; **22**: 701-704 [PMID: 12066961]

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**Table 1** **Risk factors and indications of latent tuberculosis infection treatment in the liver transplant setting (adapted from** **Meije *et al*[20] and Bosh *et al*[22])**

|  |
| --- |
| Risk factors include:1. Residence in a high-endemicity area
2. Age greater than 50 years
3. Homelessness or incarceration
4. Personal or donor history of TB
5. Diabetes mellitus, malnutrition, HIV infection, end-stage liver disease
6. Chest radiography or CT scan showing abnormalities
7. Intensification of immunosuppression for rejection; use of everolimus, sirolimus and T-cell-depleting antibodies

LTBI treatment should be prescribed to candidates with compensated cirrhosis or to recipients with normal liver allograft function and at least one of the following criteria: 1. TST (initial or after a booster effect) with an induration of ≥ 5 mm1
2. Positive IGRA result1
3. Recent change in the TST result
4. Personal or donor history of untreated or incorrectly treated TB
5. History of contact with a smear-positive TB patient
6. Residual TB lesions in an untreated patient
 |

1Only if the candidate or the recipient has not been previously treated for latent tuberculosis infection or active tuberculosis. CT: Computed tomography; HIV: Human immunodeficiency virus; IGRA: Interferon-γ release assay; LTBI: Latent tuberculosis infection; TB: Tuberculosis; TST: Tuberculin skin test.

**Table 2** **Reported fluoroquinolone-induced adverse events and outcomes associated with treatment of latent mycobacterium tuberculosis infection in liver transplantation**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Author** **[ref.]** | **Type of patients*****n* (%)** | **Treatment prescribed** | **Musculoskeletal (joint pain, tendinopathy)*****n* (%)** | **Gastrointestinal (diarrhea, vomiting)*****n* (%)** | **Constitutional (fatigue, malaise)*****n* (%)** | **Hepatotoxicity*****n* (%)** | ***C. difficile*-associated diarrhea*****n* (%)** | **Permanent withdrawal of FQ*****n* (%)** | **Completed treatment*****n* (%)** |
| Torre-Cisneros *et al*[46] | 33 LT candidates | Levofloxacin | 6 (18.2) | 3 (9.0) | 0 (0.0) | 2 (6.1) | 1 (3.0) | 11 (33.0)1 | 18 (54.5) |
| Tien *et al*[47] | 25 LT candidates and 6 additional LT recipients | Levofloxacin or moxifloxacin | 5 (16.1) | 4 (12.9) | 4 (12.9) | 0 (0.0) | 2 (6.4) | 2 (6.4)2 | 21 (67.7) |
| Grim *et al*[48]  | 8 LT and LT/KT candidates | Moxifloxacin | NA | NA | NA | NA | NA | NA | 2 (25)3 |
| Sgarabotto *et al*[49] | 35 LT recipients | Levofloxacin plus ethambutol | NA | NA | NA | NA | NA | 4 (11.4)4 | NA |

1Fluoroquinolone treatment was primarily stopped due to tenosynovitis (5 patients [45.4%]) and hepatotoxicity [2 patients (18.2%)]. 2Treatment was withdrawn due to tenosynovitis [1 patient (50.0%)] and severe constitutional symptoms [1 patient (50.0%)]. 3Data not available on the other 6 patients. 4Prophylaxis was stopped due to tenosynovitis [2 patients (50.0%)], hepatotoxicity [one patient (25.0%)], and transient optical neuritis [one recipient (25.0%)]. FQ: Fluoroquinolone; KT: Kidney transplant; LT: Liver transplant; NA: Data not available.