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Isoniazid Prophylaxis for Latent Tuberculosis Infections in Liver Transplant Recipients in a Tuberculosis-Endemic Area

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Background: Isoniazid (INH) prophylaxis (Px) has good efficacy for preventing tuberculosis (TB) in the general population. However, its use for the treatment of latent TB infections (LTBI) in liver transplant (LT) recipients is challenging because little is known about INH-induced hepatotoxicity in graft recipients. We evaluated the efficacy and safety of INH Px in LT recipients.

Material/Methods: From March 2008 to December 2012, we retrospectively reviewed data on 277 patients who received LT at a single center. We examined the results of tuberculin skin tests and interferon-γ release assays, use of INH, INH-induced hepatotoxicity, and post-LT TB occurrence.

Results: Among 277 recipients, 7 cases of post-transplant TB were detected (2.52%). Seventeen patients received post-transplant INH Px. Among INH Px recipients, post-LT TB infection did not occur. Hepatotoxicity after INH Px was significantly lower in the patients who received INH Px at an aspartate aminotransferase (AST) level that was less than 50 U/L than in those who received INH Px at an AST level that was more than 50 U/L (P=0.046, 0.002).

Conclusions: INH is likely to be effective for preventing post-LT TB recurrence in LTBI. However, because of INH-induced hepatotoxicity, it is better to avoid using it in the early post-LT period and to wait to initiate INH Px until liver function is stable in LT recipients.

MeSH Keywords: **Isoniazid • Latent Tuberculosis • Liver Transplantation**

Abbreviations: **LT** – liver transplantation; **LTBI** – latent tuberculosis infections; **Px** – prophylaxis; **TB** – tuberculosis; **TST** – tuberculin skin test; **IGRAs** – Interferon (IFN)-γ release assays

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Background

South Korea has an intermediate burden of tuberculosis (TB), reported at 90 cases per 100 000 population [1]. This incidence is higher than that in other developed countries. The incidence of TB in solid organ transplant recipients is calculated to be 20–74 times higher than in the general population [2–5]. Management of latent tuberculosis infection (LTBI) in the liver transplantation (LT) recipient is essential, because reactivation of LTBI is the most common form of TB acquisition after transplantation [3,6,7]. However, there is no general agreement on LTBI diagnosis and treatment in LT recipients [8].

Isoniazid (INH) is known to be effective for TB prevention in the general population as well as in solid organ transplant patients [9,10]. However, INH is second in the list of causative medications in the Drug-Induced Liver Injury Network (DILIN) [11]. Hayashi et al. reported that only 12% of their sample of patients with INH-induced liver injury had chronic hepatitis; the others had no background hepatic disorders [11]. The risk of INH hepatotoxicity is believed to be greater for LT recipients than for those who have not undergone LT [8]. Further, determining the cause of hepatic dysfunction is difficult because there could be many contributing factors, such as drug toxicity, rejection, allograft dysfunction, viral hepatitis, and potential drug interactions [7,8]. In the present study, we aimed to evaluate TB incidence among LT recipients and hepatotoxicity after using INH for LTBI treatment in LT recipients.

Material and Methods

Patient population

From March 2008 to December 2012, 492 living donor LTs and 137 deceased donor LTs were performed at the Samsung Medical Center in South Korea. A total of 607 patients received a primary LT in this center. However, 315 patients were excluded because they did not undergo pre-transplant interferon-γ release assays (IGRAs). An additional 15 patients were excluded: 11 died due to sepsis, postoperative complication, and primary nonfunction within 4 weeks after the LT and 4 were confirmed to have active TB during the medical work-up before LT (Figure 1). Ultimately, we reviewed data from 277 patients who underwent tests for LTBI, the tuberculin skin test (TST), and IGRAs prior to LT. Their medical records were reviewed retrospectively. We obtained data on variables such as age, sex, past TB history, date, IGRA results, TST results, use of INH, and post-LT TB occurrence. For patients who received INH Px, we reviewed additional parameters such as serum aspartate aminotransferase (AST) levels, alanine aminotransferase (ALT) levels, alkaline phosphatase (ALP) levels, total bilirubin levels, number of days from the start of INH Px to the peak AST, biopsy reports, and number of acute cellular rejection episodes.

LTBI screening

The LTBI diagnostic criteria used in this study were in accordance with the TB guidelines of the Korea Centers for Disease

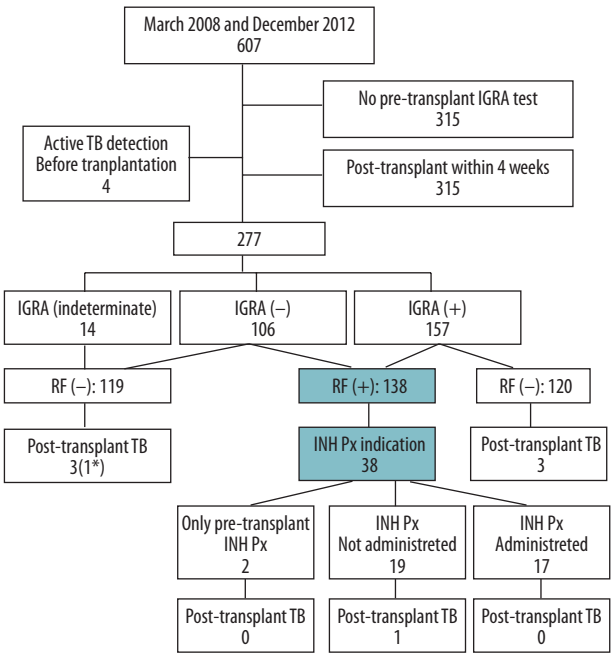

Figure 1. Flow diagram of study population and post-transplant tuberculosis in liver transplant recipients. Asterisks (*) denote donor-derived liver graft tuberculosis. IGRA – interferon-γ release assays; TB – tuberculosis; RF – risk factor (risk factors were an untreated stable TB lesion, a history of incomplete TB treatment, and a history of recent contact with a person who was diagnosed with active TB); INH – isoniazid; Px – prophylaxis.

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Control and Prevention [12]. A positive result on the TST was defined as an induration of 10 mm or more in diameter at 47–72 h after 5 tuberculin units of purified tuberculin protein derivative had been intradermally injected [12]. IGRAs (QuantiFERON® [QTF], Cellestis Ltd, Valencia, CA) were performed before LT. IGRAs were scored and represented as positive, negative, or indeterminate. Positive results were defined as interferon-γ (IFN-γ) level of nil ≤8.0 IU/mL and TB antigen minus nil ≥0.35 IU/mL and ≥25% of nil value. Negative results were defined as IFN-γ level of nil ≤8.0 IU/mL, mitogen minus nil ≥0.5 IU/mL, and TB antigen minus nil <0.35 IU/mL or <25% of nil value. The results are reported as indeterminate for IFN-γ level of nil ≤8.0 IU/mL, TB antigen minus nil <0.35 IU/mL or ≥0.35 IU/mL and <25% of nil value, and mitogen minus nil <0.5 IU/mL (positive control failure) or IFN-γ level of nil >8.0 IU/mL (negative control failure). In this study, indeterminate and negative results were combined into a single group for analysis. Chest lesions were screened with a chest X-ray, but chest computed tomography (CT) scans were performed in patients with hepatocellular carcinoma or other lung disease.

LTBI treatment

We stratified LTBI patients to low- and high-risk groups [8,13,14]. Patients with only a positive laboratory result (TST or IGRA) without any other risk factor were assigned to the low-risk group. High-risk group assignment was determined not by laboratory result (TST or IGRA), but by the following risk factors: an untreated stable TB lesion on imaging, a history of incomplete TB treatment, and a history of recent contact with a person who was diagnosed with active TB. INH Px was indicated for patients in the high-risk group. INH Px consisted of administration of 3 100-mg tablets of INH once a day for 9 months. LT recipients with LTBI were stratified for the following 2 reasons. First, INH should be administered very cautiously because of INH hepatotoxicity, which is not well understood in LT recipients. Second, we selected higher-risk LTBI patients because many of these patients had positive TST results due to previous BCG vaccination or living in TB-endemic areas.

Immunosuppression

LT recipients received a triple immunosuppressive regimen, which included a calcineurin inhibitor (tacrolimus or cyclosporine), mycophenolate mofetil (MMF), and a corticosteroid. Basiliximab (20 mg) was administered as the induction agent on the day of the operation and on postoperative (POD) day 4. Intravenous methylprednisolone (500 mg) was administered at the anhepatic phase and on POD day 1, then tapered for 7 days thereafter. The tacrolimus target trough level was 8–12 ng/mL for the first month and 5–10 ng/ml afterwards. The cyclosporine trough level was sustained at 200–300 ng/mL for the first month and was 100–200 ng/mL afterwards.

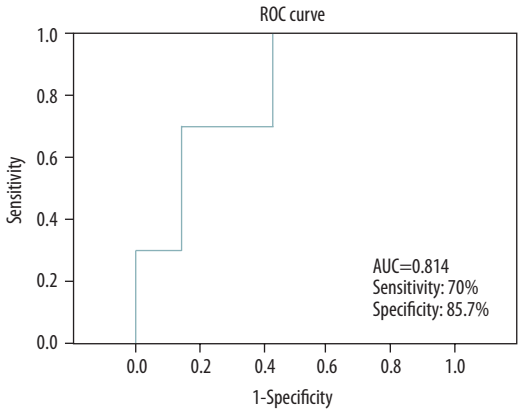

Figure 2. Receiver operating characteristic curve of 50 mg/dl of serum aspartate aminotransferase at the start of INH prophylaxis.

An MMF dose of 750 mg was started on POD day 1, and the MMF dose was subsequently tailored based on the general condition of the recipient.

Hepatotoxicity monitoring

We investigated INH hepatotoxicity in 17 patients who received INH Px after LT. The ROC curve of AST level at the start of INH indicated that an AST level of 50 U/L was the threshold value for predicting INH-related hepatotoxicity, with a sensitivity of 70% and a specificity of 85.7% (AUC=0.814, Figure 2). The 17 patients were divided into 2 groups: 9 with AST level less than 50 U/L at the start of INH Px and 8 with AST level greater than 50 U/L. We compared AST (normal: 5–40 U/L), ALT (normal: 3–40 U/L), total bilirubin (normal: 0.2–1.20 mg/dL), and POD of initiation of INH Px in both groups.

Liver function tests were performed every day of the admission period, and once per month after discharge. The increase in hepatic enzyme and bilirubin levels was graded according to severity. Grade I is 1.25–2.5 times the upper limit of normal (ULN), Grade II is 2.5–5.0 times the ULN, Grade III is 5.0–10.0 times the ULN, and Grade IV is over 10.0 times the ULN [15]. Accordingly, INH hepatotoxicity was defined as more than 5 times the normal elevation level of AST after INH administration and sign and symptom resolution after INH therapy withdrawal [15,16]. A liver biopsy was performed for patients with continuously increasing hepatic enzyme levels or when the underlying etiology needed to be clarified.

Statistical analysis

Continuous variables were expressed as either medians or ranges and were compared using the Mann-Whitney *U* test.

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Table 1. Comparison of clinical variables between patients with and without post-liver transplantation tuberculosis.

		Post-transplant TB occurrence		*P*
		No (n=270)	Yes (n=7)	
CXR lesion	Not detected	261	6	0.229
	Detected	9	1	
Chest CT lesion	Not detected	122	3	0.942
	Detected	33	1	
	Not checked	115	3	
Past history	None	234	5	0.152
	Complete Tx	15	2	
	Incomplete Tx	7	0	
	Contact	11	0	
	Unknown	3	0	
TST	Unknown	34	2	0.317
	Negative (<10 mm)	146	3	
	Positive (≥10 mm)	90	2	
IGRA	Negative	124	3	0.901
	Positive	130	4	
	Indeterminate	16	0	
LTBI treatment*	No	251	7	0.697
	Yes	19	0	

TB – tuberculosis; CXR – chest X-ray; CT – computed tomography; TST – tuberculin skin test; IGRA – interferon-γ release assay; LTBI – latent tuberculosis infection. * LTBI treatment: Isoniazid prophylaxis was indicated for LT recipients in our study on the basis of risk factors regardless of whether the TST or IGRA results were positive. The risk factors were an untreated stable TB lesion, a history of incomplete TB treatment, and a history of recent contact with a person who was diagnosed with active TB.

Fisher's exact test was used to compare categorical variables. The receiver operating characteristic (ROC) curve was used to evaluate the predictive threshold AST value for hepatotoxicity after INH Px. All reported *P* values are 2-tailed. The significance threshold was 0.05. All analyses were performed with SPSS software (version 18.0; SPSS Inc., Chicago, IL, USA).

Results

The sample included 223 male patients and 54 female patients; the median age was 52 years (1–77 years). Average Child-Turcotte-Pugh (CTP) score and Model for End-Stage Liver Disease (MELD) score were 8.3 and 16.6, respectively, and 87.0% of the LTs were a living donor LT. Table 1 shows that the positive rate of IGRAs (134/277, 48.3%) was higher than that of the TST (92/241, 38.1%) in LT recipients. Chest CT scans detected more of the old chest TB lesions (34/277, 12.2%) than chest X-rays did (10/277, 3.6%). On the basis of our LTBI treatment protocol, 38 patients needed LTBI Px. Among these 38 patients, 19 patients did not receive INH Px because of increased liver enzyme levels, hyperbilirubinemia, or post-transplant biliary or infectious complications. Two patients received INH Px before LT and 17 patients received INH Px after LT (Figure 1). The median follow-up period was 32.5 months (1.5–74.2 months).

TST and IGRA concordance

We examined the correlation between TST and IGRA. In this analysis, we excluded 36 patients because of missing or unknown TST (Table 2). The agreement between the TST and IGRA was fair and the IGRA positivity was significantly higher than the TST (κ=0.314, *P*<0.001, IGRA: 51.8% [125/241], TST: 37.3% [90/241]).

Post-transplant tuberculosis

Post-transplant TB was detected in 7 out of 277 LT recipients (2.52%). Among the 7 patients with post-transplant TB, none had received INH Px. A case of post-transplant TB was suspected to have been donor-derived TB from a living donor with latent TB (Patient 7; Table 3). Two patients had negative TST and IGRA results and none of the TB risk factors

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Table 2. TST and IGRA concordance.

		IGRA			Total	κ
		(–)	(+)	Undeterminate		
TST	(–)	84	56	9	149	0.314
	(+)	21	69	2	92	
Total		105	125	11	241	

TST – tuberculin skin test; IGRA – interferon-γ release assays. Data were analyzed with a McNemar's test and presented with a κ coefficient. In this analysis we excluded 36 patients because of missing or unknown TST.

Table 3. Case review of post-liver transplant recipients with active tuberculosis infections.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7*
Age (y)/Sex	55/M	58/F	59/M	71/M	56/M	51/M	50/M
TST	Negative	Positive	Positive	Unknown	Negative	Negative	Negative
IGRA	Positive	Positive	Positive	Positive	Negative	Negative	Negative
Chest XR	Not suspicious TB lesion	Not suspicious TB lesion	Not suspicious TB lesion	Suspicious TB lesion (+)	Not suspicious TB lesion	Not suspicious TB lesion	Not suspicious TB lesion
Chest CT	Not suspicious TB lesion	Not checked	Not suspicious TB lesion	Suspicious TB lesion (+)	Not checked	Not checked	Not suspicious TB lesion
Past history	No	Yes, completely treated	Yes, completely treated	No	No	No	No
INH Px	Not administered	Not administered	Not administered	Not administered	Not administered	Not administered	Not administered
CNI	TAC	TAC	TAC	CsA	TAC	TAC	TAC
Interval between LT and TB detection	5 months	5 months	5 months	2 months	8 months	3 months	1.5 months
Site of TB	Lung	lung, intra-abdominal	Lung	pleural	lung	lung	Graft liver, lung
Anti-TB medication	Surgical treatment was performed; patient refused medication	INH, LVX, PZA, ETB	INH, ETB, PZA, rifabutin	HERZ + rifabutin	LVX + EMB + CS	HER + levofloxacin	ETB + CS + AMK + LVX
Adverse effect of anti-TB drug	None	Blurred vision d/t ETB	Hepatotoxicity	Cytopaenia d/t INH, rifabutin	None	Arthritis	Hepatotoxicity

TST – tuberculin skin test; IGRA –interferon-γ release assays; INH – isoniazid; CNI – calcineurin inhibitor; LVX – levofloxacin; PZA – pyrazinamide; ETB – ethambutol; HERZ – isoniazid [INH], rifampin [RFP], ethambutol [EMB]; CS – cycloserine; AMK – amikacin.
* Donor-derived tuberculosis suspected.

(Patient 5, 6; Table 3). Therefore, these 2 cases were considered to be cases of community-acquired TB rather than reactivation of LTBI, even though the sensitivity of both tests is far below 100% in cirrhotic pre-transplant patients. The other 4 patients were considered as LTBI reactivation; interestingly, all of them had pre-transplant positive IGRA results (Patient 1~4, Table 3). Among them, 3 did not have any risk factors according to our LTBI treatment protocol, so they did not receive INH Px. The other one had a suspicious chest TB lesion on chest X-ray and CT. However, the patient did not receive INH Px after LT because of increased liver enzyme levels and hemobilia. Two months later, this patient visited the outpatient clinic, presenting with dyspnea. Finally, *Mycobacterium tuberculosis* was detected in the pleural fluid.

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Table 4. Hepatotoxicity in liver transplant patients with isoniazid prophylaxis.

	AST at the start of INH (U/L)		*P*
	<50, n=9	≥50, n=8	
AST at initiation of INH Px	22 (12–45)	122 (55–250)	<0.001
ALT at initiation of INH Px	40 (22–118)	277 (109–646)	<0.001
TB at initiation of INH Px	0.8 (0.3–3.7)	2.0 (0.2–3.6)	0.167
POD at initiation of INH Px (days)	33 (15–55)	4 (2–15)	<0.001
Interval between initiation of INH and the day of peak AST (days)	18 (19–98)	10 (6–18)	0.036
Peak AST after INH Px (U/L)	33 (18–203)	125 (28–418)	0.046
AST Gr III/IV	1 (11.1%)	2 (25%)	0.110
Peak ALT after INH Px (U/L)	125 (10–427)	545 (56–1506)	0.002
ALT Gr III/IV	1 (11.1%)	6 (75%)	0.014
Peak TB after INH Px	0.7 (0.5–5.0)	1.25 (0.5–2.8)	0.167
TB Gr III/IV	0	0	0.593
INH Px completion	5 (55.5%)	6 (75%)	0.620

AST – serum aspartate aminotransferase; ALT – alanine aminotransferase; TB – total bilirubin; INH – isoniazid; Px – prophylaxis; POD – post-operative day; Gr – grade.

Among the 38 patients who were subjected to LTBI treatment according to our protocol, 19 did not receive INH Px due to transplanted liver dysfunction or other complications. One of them, who was mentioned above, was diagnosed with pleural TB 2 months after LT (Figure 1). The patients had taken TB medications for 9 months. However, post-LT TB did not occur among the INH Px recipients, of whom 2 received only pre-transplant INH Px and 17 received post-transplant INH Px

In the final analysis, overall post-LT TB incidence was 2.52% (7/277; 0.02 cases for 1000 transplant days) over a median of 32.5 months. Post-LT TB incidence among low-risk LTBI recipients was about the same as post-LT TB incidence among non-LTBI recipients (2.50% *vs.* 2.15%). On the other hand, post-LT TB incidence among high-risk LTBI recipient without INH Px was relatively high, at 5.26% (1/19), and there was no TB reactivation among high-risk LTBI recipient with INH Px.

INH-induced hepatotoxicity

The overall INH hepatotoxicity rate was 17.6% (3/17). Table 4 shows that INH Px was initiated earlier in those whose AST levels were more than 50 U/L (median POD 4 *vs.* POD 33; *P*<0.001). The time interval between POD at start of INH Px and POD at peak AST after INH Px was shorter in those whose AST levels were more than 50 U/L (*P*=0.036).

Interestingly, AST level at initiation of INH Px was associated with peak elevation of INH-induced AST and ALT levels. The peak AST and ALT levels after INH Px were higher in patients whose AST levels at the start of INH Px were greater than 50 U/L compared to those whose AST levels were less than 50 U/L (*P*=0.046, 0.002). In addition, the rate of ALT grade III/IV hepatotoxicity was significantly higher in those whose AST levels were greater than 50 U/L at the start of INH Px (P=0.014). All patients with INH hepatotoxicity recovered after stopping INH Px, and there was no hepatic failure or death related to INH Px in either group.

Discussion

The overall TB incidence in the present study was 2.52% during a median of 32.5 months in LT recipients. This rate is relatively greater than the incidence of 1.3% over 53 months reported in a meta-analysis of LT recipients [17]. This relative higher rate of TB incidence indicates that the TB burden is heavier in Korea than in Western countries [13]. However, our data indicated that there was no TB occurrence among INH Px LT recipients. When INH Px was started at AST levels less than 50 U/L, INH hepatotoxicity in post-LT patients was not severe or frequent. Also, patients with hepatotoxicity recovered after stopping INH.

INH is known to be effective for TB prevention in solid organ transplant patients as well as in the general population [9,10]. Holty et al. performed a meta-analysis of TB in LT recipients; they found that INH Px was associated with a reduced

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prevalence of TB reactivation in LT candidates compared with no treatment (0% *vs.* 8.2%; *P*=0.02) [17]. Agolia et al. reported the results of INH Px in LT recipients [14]. Although INH Px was discontinued or incomplete in 20% of their sample because of suspected hepatotoxicity, there was no TB reactivation among the patients undergoing INH Px. Fabrega et al. found no differences in survival rates between LTBI patients and non-LTBI patients, as well as no severe graft dysfunction after INH initiation [18].

However, INH Px for LT recipients remains controversial because of concerns about INH hepatotoxicity [19]. Alternative approaches have been used for minimizing exposure of the new graft to INH. Singh et al. reported a case series in which INH Px was initiated during LT candidacy with good results in 2002 [20]. Jahng et al. suggested rifampin (RIF) monotherapy for 4 months as a possible alternative therapy during candidacy in 2007 [21]. However, in both case series, the patients were medically stable, with a relatively low MELD score. In addition, RIF has been known to interact with immunosuppressive drugs and should be avoided after LT [14,21]. Practically, for cases of elective living donor LT, there is not enough of a time interval between pre-transplant study and LT for Px during LT candidacy.

The differentiation point of the present study is that INH was administered on the basis of not just TST or IGRA results, but also on the identification of risk factors. LTBI treatment was indicated for patients who were stratified into the high-risk group, which included those with an untreated stable TB lesion, a history of incomplete treatment for TB, or a history of recent contact with a person who had been diagnosed with active TB. Benito et al. reported that none of the patients in their study with a positive TST result developed TB, regardless of whether they received INH. However, all 5 cases of post-LT TB in their study involved TST-negative patients [8]. They recommended considering INH Px for patients with clinical or radiological features of past TB, even if their TST results are negative [4,8]. Similarly, our policy of LTBI treatment placed more weight on clinical or radiological information. Actually, the post-LT TB infection rate in low-risk LTBI recipients who had positive TST or IGRA results without clinical or radiological features of past TB (2.50%) was similar to that of non-LTBI recipients (2.15%).

Our data show that TB did not occur among patients who received INH prophylaxis after LT. This finding supports the efficacy of INH Px, even though the results were not statistically significant (Table 1). The present study extends existing knowledge by evaluating the appropriate time and the tolerability of INH in the transplanted liver after LT. One interesting point is that there was a lower rate of INH hepatotoxicity observed in LT recipients when INH Px was started at AST levels of less than 50 U/L. This accords with the recommendation of the American Society of Transplantation, which is to delay INH initiation in LT recipients until liver function is relatively stable [22]. Another interesting point is that, out of 7 post-transplant TB recipients, excluding the 3 who were considered non-LTBI, all 4 had positive IGRA results. Therefore, it is worthwhile to investigate the efficacy of INH Px for LT recipients with only a positive IGRA result, even though we did not include IGRA results as a risk factor in the present study. According to our expectation, TST alone to confirm LTBI is excluded in the revised version of the TB guidelines of the Korea Centers for Diseases Control and Prevention, which was published in 2014 [23].

Our analysis has several limitations. First, we retrospectively reviewed and investigated LT patients who received IGRA before LT. Selection bias could have existed in this process. Second, the number of cases of post-transplant TB was too small for us to investigate the risk factors for TB, efficacy of INH Px, or post-LT TB mortality. Third, we could not repeat IGRA for patients whose IGRA results were indeterminate, because most patients had received an LT at the time the results were reported. Fourth, the number of patients receiving INH Px was not enough for us to compare hepatotoxicity and arrive at a solid conclusion. Fifth, during the INH Px period, it was difficult to determine whether the hepatotoxicity was actually attributable to INH Px. We could not completely differentiate other possible causes of hepatotoxicity, such as the effect of ischemia time, reperfusion syndrome, rejection, or other liver function problems. Finally, the American Society of Transplantation recommends treatment of LTBI before transplantation or after transplantation if an induration of ≥5 mm at 48–72 h is detected in the TST, or if QFT or T-SPOT.TB results are positive. However, we used 10 mm as a cut-off value for LTBI diagnosis according to the guidelines of the Korea Centers for Disease Control and Prevention. We could not further investigate LTBI by using 5 mm as the cut-off value, because the TST data of many patients did not have the induration size recorded and just the word “positive” was recorded.

Conclusions

Despite the limitations described in the Discussion section, our results inform LTBI management of LT recipients because few studies have examined treatment of LTBI after LT, and the risk of INH hepatotoxicity after LT is largely unknown. Another valuable contribution of the present study is that it evaluated INH hepatotoxicity and appropriate timing for INH initiation in LT recipients after transplantation. In conclusion, our study provides evidence of the efficacy and safety of INH Px for LT recipients after transplantation.

Conflict of interest statement

None.

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