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Clinical Outcomes of Tuberculosis in Recipients After Living Donor Liver Transplantation

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Background: This study aimed to determine clinical outcomes using various drugs during tuberculosis (TB) treatment among living donor liver transplant (LDLT) recipients with TB and to assess the impact of performing LDLT in patients with active TB at the time of LDLT.

Material/Methods: Out of 1313 LDLT performed from June 1994 to May 2016, 26 (2%) adult patients diagnosed with active TB were included in this study. Active TB was diagnosed using either TB culture, PCR, and/or tissue biopsy.

Results: The median age was 56 years and the male/female ratio was 1.6: 1. Most patients had pulmonary TB (69.2%), followed by extrapulmonary and disseminated TB (15.4% each). Fourteen (53.8%) patients underwent LDLT even with the presence of active TB. All patients concurrently received anti-TB [Rifampicin-based: 13 (50%); Rifabutin-based: 12 (46.2%); INH-based: 1 (3.8%)] and immunosuppressive drugs [Tacrolimus-based: 6 (23%); Sirolimus/Everolimus-based: 20 (77%)]. During treatment, adverse drug reactions (ADR) occurred in 34.6% of patients: acute rejection in 6 (23.1%), hepatotoxicity in 2 (7.7%), and blurred vision in 1 (3.8%). Twenty-three (88%) patients completed their TB treatment. Neither TB recurrence nor TB-specific mortality were observed. Three (11.5%) patients died of non-TB-related causes. The overall 5-year survival rate was 86.2%. Patients with ADRs had a higher incidence of incomplete TB treatment (log-rank: p=0.012). Furthermore, patients with incomplete treatment were significantly associated with decreased overall survival (log-rank: p<0.001). Immunosuppressive and anti-TB drugs used during TB treatment and performing LDLT in patients with active TB at the time of LDLT were not associated with ADRs and overall survival.

Conclusions: Outcomes are generally favorable with intensive peri-operative evaluation and surveillance. ADRs and incomplete TB treatment may result in poor prognosis and increased mortality rates.

MeSH Keywords: Liver Transplantation • Living Donors • Mycobacterium tuberculosis

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Background

Tuberculosis (TB) is the most commonly reported communicable disease and is a frequent opportunistic infection affecting solid organ transplant (SOT) recipients [1]. Presently, in Taiwan, where TB is endemic [2], rigorous TB treatment has led to a steady decrease in incidence even before the start of the intensive 2006 campaign [2,3]. The incidence rate of TB in Taiwan is currently equal to or lower than that of other developed Asian countries, with the exception of Japan [2–5], but it is still far higher than the rates in developed Western countries. Although the effects of this achievement may have already helped transplant recipients [6–10], these patients still have an increased risk of developing TB [6,11] and subsequently have higher risk of TB-related complications and death [6,11]. A recent nationwide, population-based, matched-cohort study comparing liver transplant (LT) patients with TB to those without TB revealed that LT patients with TB and those using mammalian target of rapamycin inhibitors (mTORi) had a higher mortality rate than those without TB and those not using mTORi [6]. In another retrospective matched-cohort study comparing transplant recipients *vs.* non-transplant recipients, transplant recipients with TB were at increased risk of anti-TB drug-associated toxicity and TB-related mortality than the matched non-transplant recipients with TB [12].

Complications experienced by LT patients with TB can make them difficult to manage [6,7]. Among these challenges, the pharmacokinetic interactions between immunosuppressive and anti-TB medications and anti-TB drug toxicities to the liver allograft are the important issues that can be actively controlled to successfully manage LT patients already diagnosed with active TB. In the pre-LT setting, on the other hand, the presence of active TB is a contraindication to transplantation. However, this may be impractical for patients needing urgent LT [13–15]. Therefore, another issue that continues to trouble patients undergoing urgent LT is the increased risk of complications and death in those who have not received prior TB treatment [8] and the increased risk of accelerated liver failure while completing TB treatment may also lead to death [1]. Because of these challenges, it has become crucial to find solutions to decrease the risk of complications and death among LT patients with active TB.

Although there are many recent studies from Taiwan addressing TB among transplant recipients and these may have already suggested possible treatment strategies [9,10,15], most of these studies included all SOT recipients and may not be entirely applicable to LT patients alone. The most recent population-based study of LT patients with TB [6] only provided a practical guide to selecting high-risk patients for regular surveillance of TB and treatment of latent TB infection. These studies did not clearly address our focus in the present study of managing LT patients already with active TB. Our study focuses on adult living donor liver transplant (LDLT) recipients, seeking to determine the clinical outcomes, the impact in overall survival, and the effect of various drugs used during TB treatment in developing complications during TB treatment and in the overall survival of LDLT recipients with active TB. Our study also aimed to determine the impact of performing LDLT in patients with active TB at the time of LDLT.

Material and Methods

Study population and data collection

A retrospective study was conducted of all adult LDLT recipients with active TB infection, either diagnosed before or after LDLT, and who have concurrently received both anti-TB and immunosuppressive medications from June 1994 to May 2016. Patients with non-active TB were not included in this study. The data were retrieved from Kaohsiung Chang Gung Memorial Hospital (KCGMH) Liver Transplantation Center's database and electronic medical records. The study population were followed up by retrieving their in-patient and out-patient records until May 2017. We collected general demographics and data related to the objectives of the study, including age, sex, LDLT indication, MELD score, Child-Pugh class, TB diagnostic modalities, TB location, timing of TB diagnosis in relation to the time of LDLT, anti-TB regimen, completeness of TB treatment, immunosuppressive drugs used during TB treatment, adverse events during TB treatment, and TB recurrence and mortality any time after TB diagnosis with their respective cause/s.

As end points, observed clinical outcomes were the development of adverse events during TB treatment and TB recurrence and death during or after TB treatment. Adverse events during TB treatment included adverse drug reactions (ADRs) and incomplete TB treatment. The definition of ADR in our study encompassed both the definition by Edwards and Aronson – "An appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment, or alteration of the dosage regimen, or withdrawal of the product" [16], as manifested by the adverse effects of anti-TB medications, and complications brought about by drug-drug interaction of concurrently using both anti-TB and immunosuppressive medications. Recipients with and without ADR were compared and differentiated in their rate of not completing TB treatment and overall survival. Patients who completed TB treatment and those who did not were likewise compared and differentiated based on their rate of overall survival. Furthermore, the study population was grouped according to the anti-TB regimen received, immunosuppressive drugs used during TB treatment, and the timing

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of TB diagnosis in relation to the time of LDLT. Intragroup comparisons were done to differentiate the rate of developing ADR and overall survival.

This study was approved by our center's Institutional Review Board (IRB no. 201800147B0).

Active TB evaluation and management in LDLT recipients

Our protocol for evaluating adult candidates being considered for LDLT has been described in detail elsewhere [17]. In October 2009 at our institution, chest computed tomography (CT) scans were introduced for routine use in candidates for LDLT. A pulmonary nodule 5 mm in diameter was used as the optimal cutoff to differentiate malignant and infectious from benign and non-infectious solitary pulmonary nodules. For a size of less than 5 mm, a follow-up of 3 months is recommended. For those over 5 mm, it is recommended to obtain pathologic diagnosis and to treat them according to the diagnosis of infectious pulmonary nodule [18,19]. A diagnosis of active pulmonary TB is based on the presence of the characteristic high-resolution CT findings [20]. In addition to the high-resolution CT criteria, as well as for the diagnosis of extrapulmonary TB, the patient must meet at least 1 of the following clinical criteria: a history of TB treatment; a history of exposure to TB; a history of previous chest imaging showing an unchanged pulmonary nodule; reactive immunological tests such as pure protein derivative (PPD) inoculation; or sputum or body fluid/tissue positive for TB on polymerase chain reaction (PCR) assay, a positive TB culture, and/or a positive tissue pathologic diagnosis [20]. The tuberculin skin test was generally used to screen for TB infection, but its low sensitivity and specificity due to a previous bacillus Calmette-Guérin (BCG) vaccination were reported. In Taiwan, a tuberculin skin test is not useful for screening TB infection due to widespread vaccination in childhood [19]. Interferon gamma release assay (IGRA) testing was also recommended in the diagnosis of TB, but recent studies have shown that its use is limited in critically ill patients [21] and is not recommended in the diagnosis of active TB infection [14]. Moreover, this test was not available in our center at the time the present patients were diagnosed with TB. Once diagnosed with active TB, LDLT candidates are further classified to "open TB" if they prove to be infectious, as demonstrated by positive sputum AFB smear, or as "non-open TB". Patients classified as having open TB are contraindicated to undergo LDLT until TB treatment has started and results of sputum AFB becomes negative, thus re-classifying the patient as non-open TB. In non-open TB patients, although it is preferred to start TB treatment prior to transplant [20], LDLT will immediately be done if the patient develops progressive liver failure or any circumstance/s that requires urgent LT. Infectious or respiratory physicians, following WHO [22] and Taiwan Center for Disease Control guidelines [23], are responsible for prescribing and, if needed, modifying anti-TB drugs. As first-line therapy, either 4- or 3-drug standard anti-TB regimens that are meant to be given for at least 6 months are used. These were Rifampicin-based regimen [Rifampicin 600 or 300 mg/day, Ethambutol (EMB) 800 or 1200 mg/day, and/or Isoniazid (INH) 300 mg/day, and/or Pyrazinamide (PZA) 1000–2000 mg/day], Rifabutin-based regimen (Rifabutin: 300 mg/day, INH: 300 mg/day, EMB: 800 mg/day and/or PZA 1500 mg/day), or INH-based regimen (INH: 300 mg/day, PZA: 1500 mg/day; EMB: 800 mg/day) [18-20]. Patients who have culture-confirmed multi-drug resistant (MDR) TB are referred to the nearest government-accredited TB center dedicated to treating and monitoring patients with MDR-TB [2].

Immunosuppression and surveillance protocol

Our post-LDLT management protocol has been described in detail elsewhere [24–26]. We routinely give basiliximab 20 mg (anti-CD25 antibodies) 6 h after portal vein reperfusion (day 0) and on post-LDLT day 4 for induction therapy. Methylprednisolone (20 mg/kg IV) is administered intraoperatively followed by 2 mg/kg/day IV administration post-transplantation and gradually tapered to oral prednisone (20 mg/daily) on postoperative day 7 until a minimum dose of 5 mg daily is achieved. Patients are weaned from steroids starting 3 months after transplantation unless these patients have had rejection episodes or if the indication for transplantation is autoimmune disease. Tacrolimus administration is delayed until renal function is improved as evidenced by adequate urine output and decreasing serum creatinine levels. Once this is achieved, oral tacrolimus (0.15 mg/kg/day) is started. Dosage adjustments were based on achieving a trough level of 10–15 ng/ml in the first week, >6 ng/ml beyond the first week and >4 ng/ml beyond the first year or even <4 ng/ml as long as there is normal liver function. Mycophenolate mofetil (MMF) is also given as part of the initial and maintenance protocol, with tacrolimus and steroids. The mean starting dose of MMF is 500 mg, twice a day. In patients with HCC or with unfavorable renal function, mTORi (Sirolimus/Everolimus) were given with or as a replacement for tacrolimus, respectively [27,28]. As per protocol, post-LDLT recipients' clinical signs and symptoms, liver function test, immunosuppressive drugs serum levels, chest x-ray, and liver ultrasound with Doppler were closely and regularly monitored. These blood exams and ancillaries are monitored daily in the early postoperative period while in the intensive care unit, every other day to weekly while in the ward, then weekly for 1 month, every 2 weeks for 1–2 months, then every 1–3 months. Immunosuppressant/s doses are increased in case of mild elevated aspartate aminotransferase (AST)/alanine aminotransferase (ALT). Liver biopsy is performed if rejection is suspected. Additional ancillaries (e.g., CT-scan and MRI/MRCP) are likewise performed depending on the initial signs and symptoms and results of the other routine tests. All of the recipients returned to our institute for lab tests, imaging

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study, and check-up at clinics [24–26]. In post-LDLT patients with active TB, the same immunosuppression and surveillance protocols are applied. In response to any clinically significant event or complication during surveillance, especially during TB treatment, anti-TB and immunosuppressive drugs are modified accordingly. Additional interventions may also be employed if the need arises.

Statistical analysis

For all collected data, continuous variables are expressed as medians and range. Categorical variables are expressed as numbers and percentages. In determining the impact of the different clinical outcomes, the cumulative incidence of not completing TB treatment and subsequent overall survival between patients with and without ADR was estimated using Kaplan-Meier method, and the difference in hazard and survival curve, respectively, were compared using the log-rank test. The same statistical tools were used in determining the impact of the anti-TB and immunosuppressive drugs used during TB treatment and the impact of performing LDLT in patients with pre-LDLT active TB, wherein the dependent variable were the development of ADR and overall survival. A p-value of <0.05 was considered significant. All statistical analyses were performed using SPSS ver. 20 (IBM SPSS Inc., Chicago, IL, USA).

Results

Demographics

Out of the 1313 LDLT recipients, 26 (2%) patients were diagnosed as having active TB and were included in this study. The median age of those LDLT recipients with TB was 56 years old. There were more males than females (male/female ratio: 1.6: 1). Indications for LDLT were mostly HCC (n=19; 73.1%) with either hepatitis B-related liver cirrhosis or hepatitis C-related liver cirrhosis or alcoholic liver cirrhosis as the underlying liver disease. The most common co-morbidity prior to LDLT were renal diseases (26.8%), which includes 5 patients with renal insufficiency, 1 with hepatorenal syndrome, and 1 with chronic renal insufficiency. The median MELD score of the recipients prior to LDLT was 11 and the Child's-Pugh classes were almost equally distributed among all recipients. The rest of the patient demographics are shown in Table 1.

Table 1. Demographics and TB characteristics.

Total n: 26	n (%)
Median Age on TB Diagnosis	56 (47–75)*
Sex (Male/Female)	16 (61.5)/10 (38.5)
Diagnosis:	
HCC (+ HBV/HCV/ALC)	19 (73.1)
HBV only	3 (11.5)
HCV only	3 (11.5)
HBV+ALC	1 (3.8)
Median MELD score**	11 (6–29)*
Child-Pugh Class	
A	9 (34.6)
B	8 (30.8)
C	9 (34.6)
TB Location	
Pulmonary alone	18 (69.2)
Extra-pulmonary alone	4 (15.4)
Disseminated	4 (15.4)
Timing of TB diagnosis	
Pre-LDLT	14 (53.8)
Post-LDLT	12 (46.2)
Anti-TB regimen	
Rifampicin based	13 (50)
Rifabutin based	12 (46.2)
Isoniazid based	1 (3.8)
Immunosuppressant used during TB treatment	
Tacrolimus based	6 (23.1)
Sirolimus based	17 (65.4)
Everolimus based	3 (11.5)

TB – tuberculosis; HCC – hepatocellular carcinoma; HBV – hepatitis B related liver cirrhosis; HCV – hepatitis C related liver cirrhosis; ALC – alcoholic liver cirrhosis; MELD – model for end-stage liver disease; LDLT – living donor liver transplant. * Range; ** did not include the +22 allotted for patients with HCC.

TB characteristics

Out of 26 LDLT recipients with active TB, 18 (69.2%) patients had pulmonary TB, followed by extrapulmonary and disseminated TB at 4 (15.4%) patients each. TB diagnosis was confirmed mostly by using TB culture (26.9%) followed by tissue biopsy (23.1%) then TB-PCR and the combination of TB-PCR + culture (19.2% each). There were 14 (53.8%) patients who were diagnosed as having active TB prior to LDLT, and none of them were classified as open TB. Three (21.4%) of these patients had already started TB treatment prior to LDLT. Of these 3, 2 of them started TB treatment 2 months pre-LDLT and 1 started 1 month pre-LDLT, then all 3 continued TB treatment after LDLT once oral intake was tolerated. The rest of the patients (n: 11, 78.5%) with pre-LDLT TB started TB treatment after LDLT once oral intake was tolerated. There was 1 (7.1%) patient from the pre-LDLT TB group who was diagnosed with MDR-TB. This patient had a history of previous pulmonary TB infection with complete treatment 6 years before LDLT. Sputum and bronchial-wash TB-PCR a few days before LDLT were negative, but there was a chest CT-scan finding of

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Table 2. Patients with adverse drug reaction during TB treatment*.

LDLT No.	Age**/ Sex	Indication	Timing of TB (from LDLT)	Anti-TB base regimen	Immunosuppressant during TB treatment	TB location	ADR	Treatment completion (duration)	Final outcome (cause of death)
563	51/F	HCV HCC	Post	Rifabutin	EVR based	Lungs	ACR	No (<2 months)	Expired (Cervical cancer)
574	64/M	HBV	Post	Rifampicin	SRL based	Disseminated (lungs + urine)	Hepato-Toxicity#	No (<2 months)	Expired (Sepsis, ARF, DIC)
632	54/M	HBV	Pre	Rifampicin	SRL based	Disseminated (lungs and ascites)	ACR	Yes (10 months)	Alive
686	48/F	HCV	Pre	Rifabutin	Tacrolimus based	Lungs	ACR	No (4 months)	Expired (re-HCV)
702	55/M	HBV HCC	Pre	Rifabutin	SRL based	Lungs	ACR	Yes (intermittent; total of 9 months)	Alive
722	59/F	HBV	Pre	Rifabutin	Tacrolimus based	Lungs	Blurring of Vision	Yes (10 months)	Alive
897	57/F	HCV	Post	Rifabutin	EVR based	Lungs	Hepato-Toxicity#	Yes (9 months)	Alive
1248	64/M	ALC HCC	Pre	Rifampicin	SRL based	Lungs	ACR	Yes (9 months)	Alive
1290	56/F	HCV HCC	Pre	Rifampicin	SRL based	Lungs	ACR	Yes (7 months)	Alive

LDLT – living donor liver transplantation; ADR – adverse drug reaction; EVR – everolimus; SRL – sirolimus; ACR – acute cellular rejection; ARF – acute renal failure, DIC – disseminated intravascular coagulation; HCV – hepatitis C related liver cirrhosis; HCC – hepatocellular carcinoma; HBV – hepatitis B related liver cirrhosis. * No TB recurrence observed on all patients; ** at TB Diagnosis; # abnormal liver function test that resulted to discontinuation of anti-TB drugs.

a 4.7-mm nodule at the left upper lung. Thoracoscopic resection of this nodule was done before LDLT. The final histopathological diagnosis of the resected nodule after LDLT was consistent with TB. This patient was started on Rifabutin-based (with INH and EMB) anti-TB regimen once oral intake was tolerated. Almost 2 months after LDLT, culture and sensitivity tests of the resected nodule revealed it to be MDR-TB. The patient was then referred to a separate government-accredited TB center. Anti-TB drugs were shifted to Streptomycin (SM), p-Aminosalicylic acid (PAS), Moxifloxacin, and Cycloserine for 2 months, then SM/PAS/Moxifloxacin/Terizidone for 6 months, followed by PAS/Moxifloxacin/Terizidone for the last 9 months of the total 17 months to complete MDR-TB treatment. This patient did not develop ADR, has completed TB treatment, has no TB recurrence, and is alive and doing well even beyond the study period. The incidence of post-LDLT TB at the time of study was 0.9% (12 of 1313 LDLT recipients), which was lower than in most TB-endemic countries (2.2–12%) and similar to the incidence rate in North America and Europe (0.6–1.4%) [7,11]. The median time to develop post-LDLT TB was 24.5 months, which was longer than the previously reported time for LT recipients in Taiwan, at 1.4 years [6]. Post-LDLT TB patients started TB treatment immediately after TB diagnosis. Most of the study population received Rifampicin-based and mTORi-based (+/– tacrolimus and/or MMF and/or steroids) regimens as their respective anti-TB and immunosuppressive drugs. The rest of the study population characteristics are shown in Table 1.

TB treatment outcomes

The median follow-up time of the study population was 49 months (range: 2–87 months) from the time of TB diagnosis. Nine (34.6%) patients developed ADR (Table 2) during TB treatment. Of these, 6 (23.1%) patients developed acute cellular rejection (ACR) that may be attributed to the known interaction between anti-TB drugs and immunosuppressive drugs [1–3], 2 patients (7.7%) developed anti-TB drug-induced hepatotoxicity, which was defined for this study as continued abnormal liver function test results attributable to the anti-TB drugs that resulted in its temporary or permanent discontinuation. One (3.8%) patient developed blurring of vision caused by EMB toxicity.

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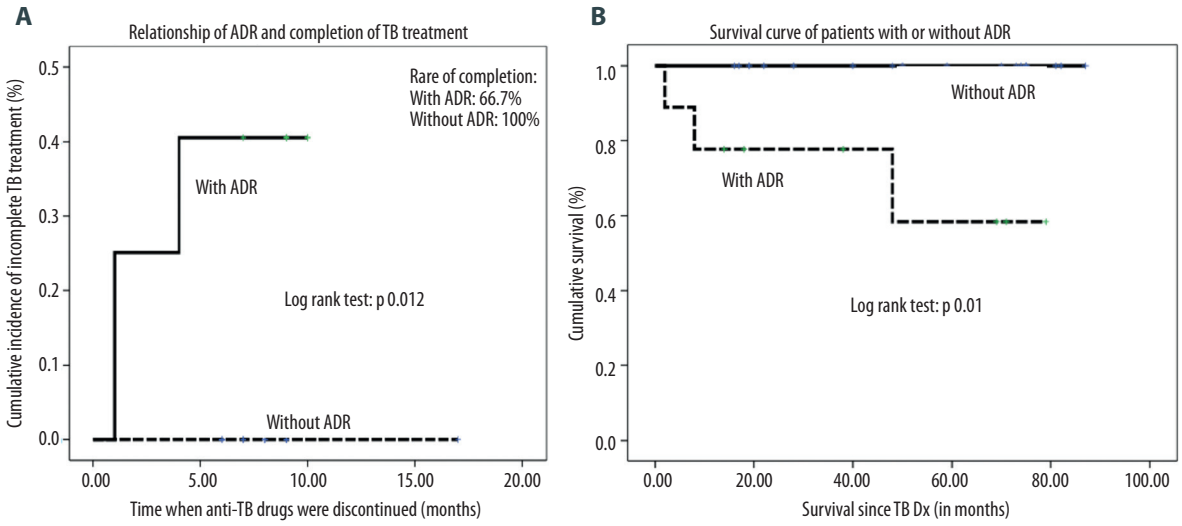

Figure 1. Comparison between patients with ADR *vs.* those without ADR in terms of (**A**) completing TB treatment and (**B**) overall survival. ADR, adverse drug reaction (during TB treatment).

Despite increasing the immunosuppressant dose and/or altering the anti-TB drugs, 3 (11.5%) patients – 2 with ACR and 1 with anti-TB drug-induced hepatotoxicity – were not able to complete TB treatment because of recurring rejections and continuous hepatotoxicity. The patient who developed blurring of vision caused by EMB toxicity was initially given Rifabutin (300 mg/day), EMB (800 mg/day), and INH (300 mg/day). Blurring of vision started 8 days after initiating TB treatment and was managed by shifting EMB to PZA, which resulted in full recovery. There was 1 patient who developed ACR 1 month after initiating TB treatment (TB drugs: Rifampicin 600 mg/day, INH 300 mg/day, and EMB 800 mg/day), who was managed by shifting Rifampicin to Rifabutin (300 mg/day), which resulted in full recovery from ACR. The rest of the patients who developed ADR were managed accordingly by increasing the dosage of the immunosuppressants and/or modifying the anti-TB medications have recovered well.

Most (23 of 26; 88.5%) patients completed their TB treatment even while concurrently taking immunosuppressive medications and remain alive by the end of the study, and there was neither TB recurrence nor TB-specific mortality. The 3 patients mentioned earlier who were not able to complete TB treatment were the same 3 (11.5%) mortality cases in which the causes of death were all unrelated to TB (Table 2). The overall median survival time from TB diagnosis until the end of the study period was 49 months. The overall 1-year and 5-year survival rates after TB diagnosis were 92.3% and 86.2%, respectively.

Prognostic significance of treatment outcomes

Kaplan-Meier analysis revealed that patients who developed ADR had a significant (33%) rate of not completing TB treatment

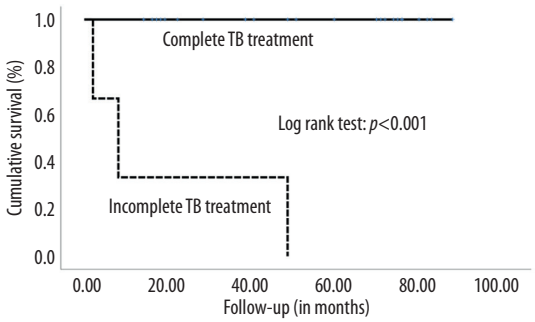

Figure 2. Survival curve of patients who completed TB treatment *vs.* those with incomplete TB treatment.

(Figure 1A) and were significantly associated with decreased overall survival (Figure 1B). Subsequently, those who were not able to complete TB treatment were significantly associated with decreased overall survival, with a median survival time of only 8 months after TB diagnosis (Figure 2).

Impact of drugs used during TB treatment

Anti-TB regimen was not significantly associated with the development of ADR (Rifabutin-based 41.7% *vs.* Rifampicin-based 30.8% *vs.* INH-based 0%; log-rank test: *p* 0.579) and overall survival (Rifabutin-based 80.2% *vs.* Rifampicin-based 92.3% *vs.* INH-based 100%; log-rank test: *p* 0.804). Immunosuppressive drugs used during TB treatment were not significantly associated with the development of ADR (SRL-based 29.4% *vs.* EVR-based 66.7% *vs.* tacrolimus-based 33.3%; log-rank test: *p* 0.313)

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and overall survival (SRL-based 94.1% *vs.* EVR-based 66.7% *vs.* tacrolimus-based 80%; log-rank test: p 0.352).

Analysis of pre-LDLT active TB patients

There were more patients diagnosed with active TB prior to LDLT than after LDLT (Table 1) due to the implementation of routine chest CT-scans in the evaluation of LDLT recipient candidates since October 2009 [18,26]. Out of the 14 patients with pre-LDLT TB, there were 4 (28.6%) patients, including the patient with MDR-TB described earlier, whose initial evaluations (i.e., TB-PCR) were negative, only to find out that the chest nodule that was removed either a day or immediately before LDLT showed positive for TB. The other 10 (71.4%) patients who were diagnosed as having active TB prior to LDLT had either progressive liver failure or had developed aggressive recurrent HCC that prompted the decision to proceed with LDLT. Three of these patients were able to start TB treatment prior to LDLT. Two received TB treatment for 2 months and the other received it for 1 month. A summary of the demographics and outcome of all pre-LDLT TB is presented in Table 3.

In comparing the outcomes of patients who underwent LDLT even based on the presence of active TB from those patients who developed active TB after LDLT, neither of the groups were significantly associated with the development of ADR (42.9% *vs.* 25%, respectively; log-rank test: p 0.347) and overall survival (89% *vs.* 83%, respectively; log-rank test: p 0.415). Likewise, in comparing those pre-LDLT TB patients who started TB treatment prior to LDLT *vs.* those who did not, neither group was significantly associated with the development of ADR (0% *vs.* 54.5%, respectively; log-rank test: p 0.132) and overall survival (100% *vs.* 83.3%, respectively; Log-rank test: p 0.480).

Discussion

Managing LDLT recipients with active TB who are concurrently receiving both anti-TB and immunosuppressive medications will always be a significant challenge. Aside from the fact that such patients were already immunocompromised as a result of both post-transplant medications and TB itself, several treatment challenges are also present. The issues that are important and must be addressed in the management of such patients were: (1) the start, duration, and completion of TB treatment, (2) the interaction of anti-TB and immunosuppressive medications, and (3) the hepatotoxic side-effect of the anti-TB medications [1,14,15,29].

As various guidelines have recommended, the presence of active TB prior to transplant contraindicates the procedure [1,8,13,30]. However, part of the challenge in managing LT candidates with on-going active TB is balancing the risks and benefits in performing LDLT or not in such patients. These patients should be closely monitored for any signs of progressive liver failure that may increase the risk of more complications and possibly death, thereby justifying performance of an urgent LDLT. As recent studies and guidelines have shown, the presence of pre-transplant active TB infection is not an absolute contraindication for SOT and may be considered for non-pulmonary SOT if the patient is receiving anti-TB treatment, has at least completed the 2-month TB treatment induction period, if sputum AFB smears are negative shortly before transplant, well controlled TB infection, and/or if patients urgently need a transplant and it is the only way to save their life [1,13–15,29–32]. There are also studies that suggested that post-transplant TB treatment may be better tolerated by the patient [1,8,33]. In our study, all patients with pre-LDLT TB, including those with unrecognized TB at the time of LDLT, were not classified as open TB. Therefore, they have negative sputum AFB smear and are not infectious. Although we were able to start TB treatment in 3 of these patients, most of them needed urgent LDLT. There were 2 main reasons why our LDLT candidates with non-open, active TB eventually underwent LDLT even without starting or completing TB treatment: (1) unrecognized TB prior to LDLT and (2) worsening liver status because of progressive liver failure and aggressive, recurrent HCC. Especially for the latter reason wherein patients urgently need LT, further delay may further increase the risk of more complications and mortality [14,15]. As our results have shown, with our current standard of care described earlier [17–20,24–26,34] and a relatively readily available living donor [32,35,36], performing LDLT in patients with active TB is not significantly associated with unfavorable outcome and may be the best option for such patients who developed accelerated liver failure or aggressive, recurrent HCC to achieve favorable outcome. In terms of completing TB treatment before transplant, studies have shown that once diagnosed with active TB prior to transplant, treatment should start as soon as possible, but it is not necessary to complete TB treatment before transplant as long as the patient is already receiving treatment and stains for the detection of acid-fast bacilli in sputum are negative when the transplant is to be performed [1,29]. Our study reaffirms that patients who started TB treatment 1–2 months prior to LDLT, then completing it after LDLT, were not associated with better outcome. However, patients who were not able to start TB treatment prior to LDLT were also not associated with the development of worse outcome.

In the consensus statement from the Group for the Study of Infection in Transplant Recipients (GESITRA) of the Spanish Society of Infectious Diseases and Clinical Microbiology, it was stated that <9 months of TB treatment was associated with greater mortality [1]. Also in the most recent guidelines, aside from increased risk of TB recurrence and increased risk of developing MDR-TB, failure to complete TB treatment carries a

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Table 3. Patients with active TB at the time of LDLT*.

LDLT No.	Age**/ Sex	LDLT Indication (MELD score)	Reason for LDLT even with active TB	Anti-TB regimen	Immunosuppressant during TB Treatment	TB Location	ADR	Start of TB Treatment Course (total duration, months)	Final Outcome (cause of death)
564	48/male	HBV HCC (11+22)	PLF	Rifampicin EMB/PZA	Tacrolimus based	Lungs	None	2 months pre-LDLT (7)	Alive
614	62/male	HBV HCC (7+22)	arHCC	Rifampicin EMB/PZA	Tacrolimus based	Lungs	None	1 month pre-LDLT (9)	Alive
632	54/male	HBV (29)	arHCC	Rifampicin INH/EMB	SRL based	Disseminated (lungs and ascites)	ACR (rifampicin shifted to rifabutin)	Post-LDLT (10)	Alive
683	52/male	HBV HCC (11+22)	Negative TB#	Rifabutin INH/EMB (shifted to SM/PAS/ MOX/TER)	SRL based	Lungs (MDR-TB; Referred to TB center)	None	Post-LDLT (20)	Alive
686	48/ female	HCV (16)	PLF	Rifabutin INH/EMB	Tacrolimus based	Lungs	ACR (stop TB Tx, several episodes of ACR)	Post-LDLT Incomplete (4)	Expired (reHCV)
698	60/ female	HBV HCC (10+22)	PLF	Rifabutin INH/EMB	Tacrolimus based	Lungs	None	2 months pre-LDLT (8)	Alive
702	55/M	HBV HCC (9+22)	Negative TB#	Rifabutin INH/EMB PZA	SRL based	Lungs	ACR (dose adjustment and several changes in anti-TB regimens, while maintaining rifabutin)	Post-LDLT Intermittent (9)	Alive
722	59/ female	HBV (25)	Negative TB#	Rifabutin INH/EMB	Tacrolimus based	Lungs	Blurring of Vision (EMB to PZA)	Post-LDLT (10)	Alive
828	65/ female	HCV HCC (12+22)	Negative TB#	Rifabutin INH/EMB PZA	EVR based	Lungs	None	Post-LDLT (6)	Alive
1242	47/male	ALC HCC (8+22)	arHCC	Rifampicin INH/EMB PZA	SRL based	Lungs	None	Post-LDLT (6)	Alive
1248	64/male	ALC HCC (12+22)	PLF	Rifampicin INH EMB PZA	SRL based	Axilla, Right	ACR (dose adjustment and several changes in anti-TB regimens, while maintaining rifampicin)	Post-LDLT (9)	Alive
1261	56/male	HCV HCC (7+22)	arHCC	Rifampicin INH/EMB	SRL based	Cervical neck	None	Post-LDLT (19)	Alive
1279	54/male	HBV HCC (7+22)	arHCC	Rifampicin INH/EMB PZA	SRL based	Lungs	None	Post-LDLT (6)	Well

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Table 3 continued. Patients with active TB at the time of LDLT*.

LDLT No.	Age**/ Sex	LDLT Indication (MELD score)	Reason for LDLT even with active TB	Anti-TB regimen	Immunosuppressant during TB Treatment	TB Location	ADR	Start of TB Treatment Course (total duration, months)	Final Outcome (cause of death)
1290	56/ female	HCV HCC (12+22)	PLF	Rifampicin INH/EMB PZA	SRL based	Lungs	ACR (dose adjustment and change of anti-TB regimen to rifampicin & INH)	YES (7 months)	Alive

LDLT – living donor liver transplantation; ADR – adverse drug reaction; HBV – hepatitis B related liver cirrhosis; HCC – hepatocellular carcinoma; HCV – hepatitis C related liver cirrhosis; ALC – alcoholic liver cirrhosis; PLF – progressive liver failure; arHCC – aggressive recurrent HCC; EMB – ethambutol; PZA – pyrazinamide; SM – streptomycin; PAS – p-aminosalicylic acid; MOX – moxifloxacin; TER – terizidone; EVR – everolimus; SRL – sirolimus; ACR – acute cellular rejection. * No TB recurrence observed on all patients; ** at TB diagnosis; # initial evaluation (i.e. TB-PCR) were negative only to find out that the histo-pathology report of the chest nodule that was removed either a day or immediately before LDLT showed positive with TB.

higher chance of mortality [1,7,8]. In our study, the duration of TB treatment among those who completed TB treatment and continued to survive was 6–18 months. All of those who were not able to complete TB treatment had only up to a maximum of 4 months of anti-TB medication, and all of these same patients subsequently died of non-TB-related causes (Table 2). With our current standard of care [17–20,24–26,34], most patients (88.5%) completed TB treatment and it is significantly associated with 100% overall survival (Figure 2).

In our study, ADR occurred in 34.6% of the total study population and the most common was the development of ACR against the liver allograft (at 23.1%), none of which resulted in graft loss. Due to its potent sterilizing activity, Rifampicin remains a first-line drug against TB [22]. However, when used in combination with immunosuppressive drugs such as calcineurin inhibitors (CNI), mTORi, and corticosteroid, since it is a potent inducer of cytochrome P3A4, it significantly reduces blood levels of these immunosuppressive drugs [7,37]. It was also stated in another study that interactions between Rifampicin and these types of immunosuppressive drugs were associated with high risk of graft rejection, graft loss, and overall TB mortality [1]. Moreover, aside from inducing cytochrome P3A4, Rifamycin derivatives (Rifampicin, Rifabutin, and Rifapentine) are also inducers of uridinediphosphate-glucuronosyltransferases (UGTs), monoamine oxidases, and glutathione S-transferases [38]. UGTs play an important role in the metabolism and disposition of MMF; therefore, induction of UGTs activity can lead to significant MMF underexposure and loss of clinical efficacy, resulting in acute or chronic graft rejection [39,40] and in some reports, using MMF alone in transplant patients with TB is not associated with better outcomes compared with calcineurin inhibitors (CNI) [41] and is associated with TB recurrence [42]. Several methods are recommended to counter these effects.

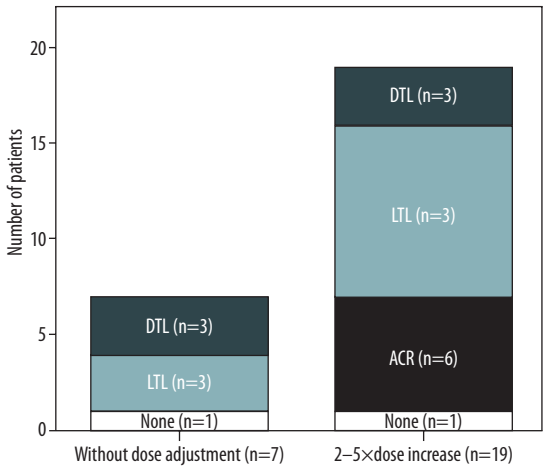

Figure 3. Results of anti-TB-immunosuppressant interaction of patients with and without Immunosuppressant Dosage Adjustment During TB Treatment. DTL – decreased trough levels (still within therapeutic level); LTL – low trough level (below therapeutic level); ACR – acute cellular rejection.

One of the most common recommendations is to increase the dosage of the immunosuppressants to 2–5 times the usual dose and combine it with close and regular monitoring of the blood level [7,8,14,29,30,37,39,40]. In our study, following our protocol of using multi-immunosuppressant combination, as described above, 19 (73%) patients received an increase (2–5×) dose of immunosuppressants during TB treatment, with or without the development of decreased immunosuppressant trough levels (Figure 3). In a subset analysis comparing those patients who received only the usual dose *vs.* those who received increased

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doses of immunosuppressants, the "usual dose" patients were not associated with the development of ACR (0% *vs.* 31.6%, respectively; log-rank test: *p* 0.113), not completing TB treatment (14.3% *vs.* 10.5%, respectively; log-rank test: *p* 0.778), and overall survival (85.7% *vs.* 86.1% respectively; log-rank test: *p* 0.768). Immunosuppressant dose adjustments and modification of anti-TB drugs, as described earlier, were done automatically and as a response or intervention to the close and regular monitoring of both immunosuppressant trough levels and liver function. In our center, with our immunosuppression protocol using the combination of tacrolimus/mTORi with MMF and/or steroids that generally resulted in excellent outcomes for all our LDLT cases [36,43], monotherapy with any immunosuppressant in LDLT patients with TB was not considered. In the present study, with our current standard of care of close and regular monitoring and prompt intervention [17–20,24–26,34], although the trend is in favor of increasing immunosuppressant dose, it may not be necessary to automatically increase the dose of immunosuppressive drugs while LDLT recipients are concurrently receiving mostly rifamycin-based anti-TB regimen. Even for those with ACR and those whose immunosuppressant dose were not increased during TB treatment, most patients were able to tolerate concurrent intake of both anti-TB and immunosuppressive drugs, thus completing TB treatment. With these findings and this study's limitations, we highly recommend further studies with better study design to assess the value of automatically increasing immunosuppressant dose, even without the actual need for it.

Another recommendation is to use Rifabutin instead of Rifampicin, which has the same potency against TB but has lesser effect on cytochrome P3A4 [1,8,14,30]. In our study, there was no significant association between the use of different anti-TB regimens (Rifampicin-based, Rifabutin-based, INH-based) and the development of ADR or overall mortality. Although most publications recommended the use of Rifabutin-based regimens [1,14,30,44], there were others that noted no difference in post-TB rejection rate and mortality between patients who received Rifampicin from those who received Rifabutin-based regimens [8,45]. Generally, there are still relatively few published clinical reports on use of Rifabutin after transplantation [7]. It is therefore recommended to perform further studies to directly compare the outcomes of using Rifabutin *vs.* Rifampicin in LDLT patients with active TB.

Mieje et al. showed that the risk of hepatotoxicity is greater when INH is used in combination with other anti-TB drugs [8]. An additional recommendation, especially in LT recipients, this time to address anti-TB drug-induced hepatotoxicity, is the use of non-Rifamycin (Rifampicin or Rifabutin) regimens, especially for non-severe and localized forms of TB. In doing this, treatment duration should be extended to 12–18 months. However, in patients with severe or disseminated TB, either Rifampicin or Rifabutin should still be used [8]. In our study, although most of the patients had non-severe, localized forms of TB, most of them received either Rifampicin or Rifabutin together with INH, EMB, and/or PZA. This, however only resulted in 7.7% (2 of 26) anti-TB drug-induced hepatotoxicity that resulted to discontinuation of anti-TB drugs and was neither significantly associated with any of the anti-TB regimen nor immunosuppressants used during TB treatment. These findings further emphasized the importance of close monitoring and early intervention in such patients [14,15].

All of our LDLT recipients received thorough pre-LDLT evaluation and intensive post-LDLT surveillance. A significant part of our patient surveillance is focusing on the immunosuppressant trough levels and liver function, which are also very important in the surveillance of LDLT recipients with active TB [1,7,8,30]. The clinical signs and symptoms and chest images are likewise very important during surveillance, as this will drive further examinations to confirm diagnosis and effectively treat TB recurrence [7,8]. With our current standard of care for all our LDLT recipients [17–20,24–26,34], this resulted in a 88.5% TB treatment completion rate, a 58.3% overall survival estimate for those with ADR (Figure 1B), and an overall 5-year survival rate of 86.2%, which are better than the other reported studies outside Taiwan [6,7,11] and in Taiwan [6,9,10,15]. Patients who completed TB treatment have a 100% overall survival rate (Figure 2). However, this study has its limitation. Data collection was done retrospectively from a single institution. Data collection was likewise highly dependent on the available information, which was recorded long before this study started and in our routine practice setting.

Conclusions

All post-transplant recipients with active TB are known to have increased risk of complications and death, and managing such patients requires effectively balancing the benefits of concurrent intake of anti-TB and immunosuppressive medications and the risk of graft rejection, TB drug- induced toxicity, and death. Although the results showed that performing LDLT in patients with concurrent active TB, at least 6 months duration of TB treatment, the choice of anti-TB regimen and immunosuppressive drugs, and only increasing the immunosuppressant dose as needed (during close follow-up) were not associated with poor outcome, those with ADR and who did not complete TB treatment were significantly associated with poor outcome. Our study further emphasizes the importance of thorough evaluation, intensive surveillance, and prompt intervention in such patients. With our standard of care in pre-LDLT evaluation and post-LDLT surveillance, clinical outcomes of LDLT recipients with active TB were mostly favorable. Complications were detected early and appropriate interventions were given promptly. This standard practice can increase the likelihood of successfully managing ADR, completing TB treatment, and thereby possibly increasing overall survival.

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