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Tuberculosis Outcome in Solid Organ Transplant Recipients

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Abstract

Objectives: Limited data are available on tuberculosis outcome after solid organ transplantation in the Middle East. Between 2005 and 2016, tuberculosis was diagnosed in 42 (1.4%) out of 3,042 kidney, liver or heart transplant recipients. Therefore, we aimed to describe the epidemiology, clinical characteristics, treatment and outcome of TB in the setting of SOT in one of the largest transplant centers in the Middle East and North Africa region.

Material and Methods: Details of kidney, liver or heart transplant recipients were retrospectively retrieved from the electronic database of the Organ Transplant Center at King Faisal Specialist Hospital and Research Centre, Riyadh. Active tuberculosis was defined as cases treated for tuberculosis based on microbiological results, radiological and/or clinical features suggestive of tuberculosis.

Results: Median age was 54.5 years (range 20–67) and 81% were males, and median time from transplant to tuberculosis was 14.6 months (0.5–255.8). Thirteen (31.0%) were recipients of organs from deceased donors. Fever (71.4%) and weight loss (57.1%) were the commonest presenting symptoms. In 26 patients (61.9%) rifampin and/or pyrazinamide were substituted with moxifloxacin. Hepatotoxicity-related treatment interruption occurred in 13 (31.0%) patients. Overall mortality was noted in Six (14.3%) patients within 12 months of tuberculosis diagnosis (none were tuberculosis related). Age (adjusted OR 0.892, 95% CI 0.827–0.961; P 0.003) and Charlson Comorbidity Score (adjusted OR 2.866, 95% CI 1.331–6.174; P 0.007) were independently associated with all-cause mortality at 12-months. Overall, mortality was higher in liver (25.0%) compared with kidney (9.1%) and heart transplant recipients (0%), but the difference was not statistically significant (log rank P 0.51).

Conclusions: Moxifloxacin-based anti-tuberculous therapy in post-SOT tuberculosis is associated with low rates of hepatotoxicity interruptions: low mortality and no graft rejection.

Keywords: Tuberculosis; Solid organ transplant; Graft rejection; Clinical Presentation: Clinical outcomes; immunosuppressant

Introduction

Solid Organ Transplantation (SOT) is an established therapeutic option for end-stage dysfunction of a variety of organ systems [1]. In the year 2017, more than 139,000 SOT were performed worldwide [2]. Progressive development in surgical techniques, newer and safer immunosuppressant medications, as well as improved prevention, diagnosis and management of infectious complications have all contributed to improved clinical outcomes and survival of organ recipients [1,3]. Tuberculosis (TB) continues to be a major concern in many parts of the world. The most recent global World Health Organization report estimates that 10 million new TB cases occurred in the year 2018 [4]. In SOT recipients, the incidence of TB is 4–30 times higher than that in the general population [5]. The incidence of TB is also relatively high in individuals with end-stage end organ dysfunction patients who are awaiting transplantation [6]. Tuberculosis in SOT occurs as a consequence of reactivation of old infection or, less commonly, as donor derived infection [5]. Management of TB in SOT is challenging owing to atypical presentation, absence of the classical radiological signs and the significant drug-drug interaction between anti-tuberculous and immunosuppressant medication [7-9]. Hence, TB-associated mortality in SOT recipients is reported to be as high as 18-30% [6,7,10,11]. There are limited data on TB in SOT recipients from the Middle East and North Africa (MENA) region [12,13]. Our aim was to describe the epidemiology, clinical characteristics, treatment and outcome of TB in the setting of SOT in one of the largest transplant centers in the MENA region.

Methods

Details of kidney, liver or heart transplant recipients were retrospectively retrieved from the electronic database of the Organ Transplant Center at King Faisal Specialist Hospital and Research Centre, Riyadh. Patients of any age were included in the study if they received one of these organs during the period between January 1, 2005 and December 31, 2016 and were treated for active TB after the transplantation.

Active TB was defined as cases treated for TB based on microbiological results (positive acid-fast bacilli culture or Mycobacterium TB PCR (GeneXpert MTB/RIF, Cephid, Sunnyvale, California, USA), radiological and/or clinical features suggestive of TB. Clinical, laboratory and radiological data were extracted. Mortality at 30 days, 90 days and 12 months were collected. The study was approved and need for informed consent was waived by the Institutional Review Board.

Data were summarized using medians and ranges or numbers and frequencies, as appropriate. Chi-square and Mann Whitney tests were used to compare clinical characteristics of SOT recipients who survived for 12 months or more after initiation of anti-tuberculous therapy versus those who did not. Variables with an associated P value of less than 0.05 were included in a multivariate logistic regression analysis for all-cause mortality at 12 months. Kaplan-Meier curve was

used to compare survival in recipients of different organ types. All analyses were performed using Statistical Package for the Social Sciences (SPSS) for Mac, Version 21 (IBM Corporation, Armonk, New York, United States).

Results

A total of 42 patients were included, 22 (52.4 %) were kidney, 16 (38.1 %) were liver and 4 (9.5%) were heart transplant recipients. The majority of the patients were males (34, 81.0%) with a median Charlson Comorbidity Score of 2 (range 0 – 7) at the time of TB diagnosis. A summary the baseline demographic and clinical characteristics of the patients is presented in Table 1.

Variables	Total (n=42)	Liver Transplant Recipients (n=16)	Kidney Transplant Recipients (n=22)	Heart Transplant Recipients (n=4)
Median age (range)	54.5 (20-67)	58.5 (27-67)	51 (20-65)	42 (28-45)
Male gender (n, %)	34 (81.0%)	15 (93.7%)	16 (72.7%)	3 (75.0%)
Median weight (range)	55.9 (38-105)	58.5 (39.5-87)	55.4 (38-105)	56 (51-72)
Diabetes mellitus (n, %)*	21 (50. 0%)	10 (62.5%)	10 (45.6%)	1 (25.0%)
Renal dysfunction (n, %)*	15 (35.7%)	7 (43.7%)	6 (27.2%)	1 (25.0%)
Median CCS (range)	2 (0-7)	3 (0-7)	2 (0-6)	1 (0-2)
History of TB exposure number (n, %)	5 (12.0%)	4 (24.0%)	1 (4.5%)	0 (0%)
Prior history of TB (n, %)	5 (12.0%)	0 (0%)	4 (18.2%)	1 (25.0 %)
Pre-transplant TST/QuantiFERON-Tb Gold testing (n, %)	20 (47.6%)	11 (68.7%)	7 (32.0%)	2 (50.0%)
Pre-transplant positive TST/QuantiFERON Gold (n, %)	9 (45.0%)	6 (45.5%)	2 (25.5%)	1 (50.0%)
Pre-transplant latent TB treatment (n, %)	1 (2.4%)	0 (0%)	1 (4.5%)	0 (0%)
Transplant performed in Saudi Arabia (n, %)	30 (71.4%)	14 (87.5%)	12 (54.5%)	4 (100.0%)
Deceased donors (n, %)	13 (31.0%)	6 (60.0%)	3 (14%)	4 (100.0%)
Receipt of induction immunosuppression agent, n (%)	23 (54.8%)	11 (68.8%)	8 (36.4%)	4 (100.0%)
ATG (n, %)	10 (23.8%)	0 (0%)	6 (27%)	3 (75.0%)
Basiliximab (n, %)	6 (14.3%)	6 (37.5%)	0 (0%)	0 (0%)
Methylprednisone (n, %)	14 (33.3%)	8 (50.0%)	3 (13.6%)	4 (100.0%)
Receipt of more than one induction immunosuppression agent (n, %)	7 (16.7%)	3 (18.8%)	1 (4.6%)	3 (75%)
Requirement for renal replacement therapy after transplant (n, %)	5 (12.0%)	4 (25.0%)	1 (4.5%)	0 (0%)
Requirement for mechanical ventilation after transplant (n, %)	15 (35.7%)	13 (81.3%)	1 (4.5%)	0 (0%)
Median months to TB diagnosis (range)	14.6 (0.5-255.8)	9.7 (0.5-77.4)	39 (1.7-255.8)	17.7 (2.3-58.8)
Site of involvement				
Miliary (n, %)	5 (12.0%)	1 (6.3%)	4 (18.2%)	0 (0%)
Isolated pulmonary (n, %)	13 (31.0%)	9 (56.2%)	3 (13.6 %)	1 (25.0%)
Multifocal with pulmonary involvement (n, %)	11 (26.2%)	3 (18.8%)	7 (31.8 %)	1 (25.0 %)
CNS involvement (n, %)	2 (4.8 %)	0 (0%)	2 (9.1 %)	0 (0%)

Peritoneal (n, %)	1 (2.4 %)	1 (6.3%)	0 (0%)	0 (0%)
Allograft involvement (n, %)	3 (7.1 %)	2 (12.5%)	1 (4.6%)	0 (0%)
Testicular (n, %)	1 (2.4 %)	0 (0%)	1 (4.6 %)	0 (0%)
Other sites (n, %)	7 (16.7 %)	0 (0%)	5 (22.8 %)	2 (50.0%)
Presenting symptoms				
Fever (n, %)	30 (71.4%)	9 (56 %)	18 (81.8%)	3 (75.0%)
Weight loss (n, %)	24 (57.1%)	7 (43.7%)	16 (72.7%)	1 (25.0%)
Cough (n, %)	13 (31.0%)	7 (43.7%)	6 (27.8%)	0 (0%)

Table 1: Demographic and clinical characteristics of the patients with active tuberculosis following liver: kidney or heart transplantation.
*At time of TB diagnosis; ATG: anti-thymocyte globulin; CCS: Charlson Comorbidity Score

Active TB was diagnosed in 16 (1.7%) out of a total of 918 patients who underwent liver transplantation during the study period. Chronic viral hepatitis (8, 50.0%) was the commonest indication for liver transplantation, followed by schistosomiasis (3, 18.8%), autoimmune hepatitis (3, 18.8%) and cryptogenic liver cirrhosis (2, 12.5%). The median Model for End-Stage Liver Disease (MELD) score at the time of liver transplantation was 19 (range 13 - 44). Over one half (9, 56.3%) of the liver recipients with active TB received grafts from living-related donors. Among those, 2 (12.5%) of the donors had undergone pre-transplant QuantiFERON-TB Gold (QFT) (Qiagen, Germantown, Maryland, United States) testing; and both donors had negative tests. The remaining 7 (43.8%) liver recipients received organs from deceased donors; 2 in China from Chinese donors, while the nationalities of the other 5 donors are not available. The majority (11, 68.8 %) of the liver recipients received induction immunosuppressive regimen; 3 with basiliximab, 5 with methylprednisone and 3 with both agents. Ten patients (62.5%) were on triple immunosuppressant medications with tacrolimus, mycophenolate mofetil and prednisone, while the other 6 patients (37.5%) were on 2 immunosuppressants at the time of TB diagnosis.

Twenty-two (1.2%) out of 1,906 individuals who underwent kidney transplantation during the study period were diagnosed with post-transplant active TB. Most had end-stage renal disease secondary to diabetes mellitus (5, 22.7 %), hypertension (10, 45.5%), or idiopathic causes (7, 31.8%). Glomerulonephritis, vesicoureteral reflux, drug-induced kidney injury and congenital causes contributed to 5 (22.7%) cases. The median time on dialysis prior to transplant was 7 months (range 0 – 84). Nineteen patients (86.4%) had organs from living donors. Eight patients (36.3%) received induction immunosuppression with anti-thymocyte globulin (ATG) in 5 patients, methylprednisone in 2 patients and both agents in 1 patient. Other patients had no clear documentation of receiving induction immunosuppression therapy, mostly because they were transplanted in centers outside Saudi Arabia (9, 40.9%). Fifteen patients (61.2%) were on triple immunosuppressant medications with tacrolimus (or cyclosporine), mycophenolate mofetil and prednisone, while 7 (31.8%) patients were on 2 (9.1%) immunosuppressants at the time of TB diagnosis.

Only 4 (1.8%) out of 218 patients who underwent heart transplantation during the study period developed post-transplant TB. Three (75.0%) patients had idiopathic cardiomyopathy and 1 (25.0%) patient had dilated cardiomyopathy. All patients received induction immunosuppression with ATG; 3 patients received concomitant methylprednisone induction. All 4 patients were on triple immunosuppressant medications with tacrolimus (or cyclosporine), mycophenolate mofetil and prednisone at the time of TB diagnosis.

Overall, the median time between transplant and TB diagnosis was 14.6 months (0.5–255.8). A total of 17 patients (42.5%) were diagnosed within the first 12 months after transplant; 11 (64.7%) of these received 1 induction immunosuppressive agent, while 2 patients received 2 agents. Liver transplant recipients constituted 47.1% of the patients who were diagnosed in the first year. Only 5 (29.4%) patients were transplanted abroad (2 in Pakistan, 1 in Lebanon, 1 in China and 1 in the Philippines). Five out of the 17 (29.4%) patients had positive QFT prior to transplant and never received TB chemoprophylaxis.

Among the 25 patients who were diagnosed after the first year of transplant, 11 patients (44%) were on triple immunosuppressant medications at the time of TB diagnosis. Three patients had positive QFT and were diagnosed during the second year of transplant. One patient had a positive tuberculin skin test (TST). This patient received TB chemoprophylaxis at the time of transplantation but developed active TB 20 years later.

Majority of patients (29,69.0 %) of the patients in this cohort were on 3 immunosuppressant medications at the time of TB diagnosis; (29, 69.0 %) were on tacrolimus-based immunosuppressant regimens while (13, 31.0 %) were on cyclosporine-based regimens.

Lungs were the most common site of involvement (29, 69.0%); 13 (44.8%) of these had isolated pulmonary involvement. Graft involvement was seen in only 3 (7.1%) patients, 2 patients with liver transplant and 1 patient with kidney transplant. Both liver transplant patients received organs from deceased donors. Kidney transplant recipients constituted 90.0% (4 out of 5) of those who presented with miliary and 63.6% (7 out of 11) of those with multifocal TB.

Fever was present at presentation in most patients (30, 71.4%). One half (21, 50.0%) of the patients presented with both fever and weight loss. Cough was present in 8 (44.4%) of those with pulmonary involvement, while both cough and shortness of breath were reported in 19 (65.5%) patients with lung involvement. Fever accompanied by weight loss and anorexia were the commonest presenting symptoms (27, 64.3%) in patients with miliary or multifocal TB.

TB was suspected clinically in the majority of patients (31, 73.8%) and was confirmed microbiologically in 36 (85.7%) of the patients in this cohort. Results of the microbiological tests are summarized in

Table 2. Among patients with pulmonary involvement, sputum Ziehl-Neelsen (ZN) stain was positive in 13 (46.4%) out of 28 patients. Interestingly, sputum ZN was positive in 3 (60.0%) patients with miliary TB. PCR and mycobacterial cultures were positive in 7 (24.1%) and 24 (82.8%) out of 29 patients with pulmonary involvement, respectively. The diagnosis in the remaining 4 patients was achieved by positive Broncho-alveolar lavage (BAL) cultures in 2 patients and positive cultures from other sites in 2 patients. In patients with miliary TB, the disease was confirmed microbiologically in 4 out of 5 patients. All 4 had positive sputum cultures and 3 had positive BAL cultures. Two kidney transplant patients with miliary TB had positive urine cultures as well. The 2 patients with liver allograft infection had positive ZN stain and culture from liver tissue. Biopsy for histology was done in 15 out of 42 patients (35.0%). Necrotizing granulomatous changes were reported in biopsies from 10 (66.7%) patients and positive ZN stain on histology from 7 (46.7%) recipients.

Sample	ZN stain on pulmonary samples (sputum/BAL)	PCR on pulmonary samples (sputum/BAL)	Culture on pulmonary samples (sputum/BAL)	ZN on extra-pulmonary samples	PCR on extra-pulmonary samples	Culture on extra-pulmonary samples
Number positive	16	7	25	9	5	22
Liver transplant	7	5	13	6	3	8
Kidney transplant	8	1	10	2	1	13
Heart	1	1	2	1	1	1

Table 2: Microbiological confirmation of tuberculosis in recipients of liver: kidney or heart transplantation.
BAL: bronchoalveolar lavage; PCR: polymerase chain reaction; ZN: Ziehl-Neelsen

The majority of patients received modified first line therapy (26, 62.0%). Treatment regimens are summarized in Table 3. All liver transplant recipients received modified first line therapy; the majority of which did not include pyrazinamide (PYZ). Fluoroquinolones (FQ) were used as a substitute for PYZ in 16 patients (8 liver, 7 kidney and 1 heart transplant recipient) and as substitute for rifampin (RIF) in 7 patients (4 liver transplant, 1 kidney and 2 heart transplant). Hepatotoxicity developed in 13 (31.0%) recipients (5 liver and 8 kidney transplant recipients). Management of patients who developed hepatotoxicity is summarized in Table 4. Notably, agents that were associated with hepatotoxicity were successfully re-introduced in 7 (53.8%) of those 13 recipients.

	Total cohort (n=42)	Liver transplant recipients (n=16)	Kidney transplant recipients (n=22)	Heart transplant recipients (n=4)
RIF-sparing regimens (n, %)	7 (16.7%)	4 (25.0%)	1 (4.5%)	2 (50.0%)
PYZ-sparing regimens (n, %)	24 (57.1%)	12 (75.0%)	9 (41.0%)	1 (25.0%)
FQ-based regimens (n, %)	33 (78.6%)	14 (87.5%)	16 (72.7%)	3 (75.0%)

Table 3: Modified anti-tuberculous regimens received by patients with active tuberculosis following liver: kidney or heart transplantation
ATT anti-tuberculous therapy; CNI: calcineurin inhibitors; CsA: cyclosporine; CS: cycloserine; EMB: ethambutol; INH: isoniazid; IS: immune suppressant; LZD: linezolid; LFX: levofloxacin; MXF: moxifloxacin; PYZ: pyrazinamide; RIF: rifampin; FQ: fluoroquinolones; PYZ: pyrazinamide; RIF: rifampin

Organ transplanted	Age	CNI based IS regimen	Initial ATT	Modification	Intensive phase	Continuation phase	Total duration of ATT in months
Liver	64	Tacrolimus	INH	Rifampin stopped	INH	INH	9
			RIF		PYZ	EMB	
			PYZ		EMB	MXF	
			EMB		MXF		
			MXF				
Liver	64	Tacrolimus	INH	INH and RIF stopped then resumed again	INH	INH	6

			RIF		RIF	RIF	
			EMB		EMB		
			MXF		MXF		
Kidney	60	Tacrolimus	INH	Switch RIF to MXF	INH	INH	Died at 4 months
			RIF	PYZ stopped	EMB	MXF	
			PYZ		MXF	EMB	
			EMB		Amikacin		
Liver	60	Tacrolimus	INH	INH and RIF stopped	Amikacin	INH	Died at 5 months
			RIF	Amikacin started	EMB	RIF	
			EMB	Re challenged with RIF and INH	MXF		
			MXF		INH resumed		
Liver	59	Tacrolimus	INH	All first line agents were stopped and started on amikacin/MXF and Imipenem for 2 weeks	INH	INH	12
			RIF	INH and RIF were re-introduced	RIF	RIF	
			PYZ		MXF	MXF	
			EMB				
Kidney	55	CsA	INH	RIF switched to MXF	INH	INH	9
			RIF		PYZ	MXF	
			PYZ		EMB	EMB	
			EMB		MXF		
Kidney	55	Tacrolimus	INH	RIF stopped towards the end of treatment	INH	INH	9
			RIF		RIF	RIF	
			PYZ		PYZ		
			EMB		EMB		
Liver	51	Tacrolimus	INH	RIF and PYZ stopped	INH	LZD	18
			RIF		LZD	EMB	
			PYZ		EMB	LFX	
			EMB		LFX		
Kidney	51	Tacrolimus	INH	PYZ stopped	INH	INH	12
			RIF		RIF	RIF	
			PYZ		PYZ		
			EMB		EMB		
Kidney	49	CsA	INH	All stopped then INH and EMB	INH	INH	18

			RIF	restarted and MXF added	EMB	EMB	
			PYZ		MXF	MXF	
			EMB				
Kidney	49	CsA	INH	All stopped and started on amikacin: EMB and MXF	Amikacin EMB MXF	EMB	18
			RIF	INH resistant	PYZ	MXF	
			PYZ			PYZ	
			EMB			CS	
Kidney	48	Tacrolimus	INH	All stopped then resumed on INH with EMB and MXF	INH	INH	9
			RIF		EMB MXF	RIF	
			PYZ				
			EMB				
Kidney	47	CsA	INH	Toxicity after intensive phase	INH	INH	7
			RIF	PYZ and EMB stopped	RIF	RIF	
			PYZ		PYZ		
			EMB		EMB		

Table 4: Treatment of the 13 patients who developed hepatotoxicity

Smear conversion was documented in 9 (69.2%) patients with positive initial ZN stains: while mycobacterial culture conversion was demonstrated in 16 (66.7%). Patients were treated for a median duration of 9.5 months (1–36). Six patients were treated for less than 6 months; 3 died within 90 days and 3 died within the first year of transplant.

Overall: 6 (14.3%) patients died within the first year of diagnosis. Compared with those who survived for more than 12 months after diagnosis of TB: patients who died were significantly older (median age 60 versus 51 years: P = 0:033) and had higher median Charlson Co-morbidity Scores (6 versus 2: P = 0.001) (Table 5). Age (adjusted odds ratio 0.892: 95% confidence interval 0.827–0.961; P 0.003) and Charlson Comorbidity Score (adjusted OR 2.866: 95% CI 1.331–6.174; P 0.007) were independently associated with all-cause mortality at 12-months. All-cause mortality at 36 months was higher in liver transplant (25.0%) compared with kidney transplant (9.1%) and heart transplant recipients (0%): but the difference was not statistically significant (log rank P 0.51) (Figure 1).

Factor	Dead (n=6)	Alive (n=36)	P value
Age (years median, range)	60 (51-64)	51 (20.0-67.0)	0.033
Weight (kg median, range)	47.0 (39.5-63.0)	56.4 (38.0-93.3)	0.235
CCS (median, range)	6.0 (4.0-7.0)	2.0 (0-7.0)	0.001
Male gender (n, %)	6 (100.0%)	28 (77.8%)	0.576
Diabetes mellitus (n, %)	5 (83.3%)	16 (44.4%)	0.184
Liver transplant (n, %)	4 (66.6%)	12 (33.3%)	0.18
Kidney transplant (n, %)	2 (33.3%)	20 (55.6%)	0.4
Heart transplant (n, %)	0	4 (11.1%)	1
TB within ≤12months of transplant (n, %)	1 (16.7%)	16 (44.4%)	0.374

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Miliary TB (n, %)	0	5 (13.9%)	1
Pulmonary involvement (n, %)	4 (66.7%)	25 (69.4%)	1
Hepatotoxicity (n, %)	3 (50.0%)	10 (27.8%)	0.353
Modified ATT (n, %)	5 (83.3%)	21 (58.3%)	0.38

Table 5: Bivariate analysis for all-cause mortality at 12 months after diagnosis of active TB in liver: kidney or heart transplant recipients
ATT: Anti-Tuberculosis Therapy; CCS: Charlson Comorbidity Score; TB: Tuberculosis

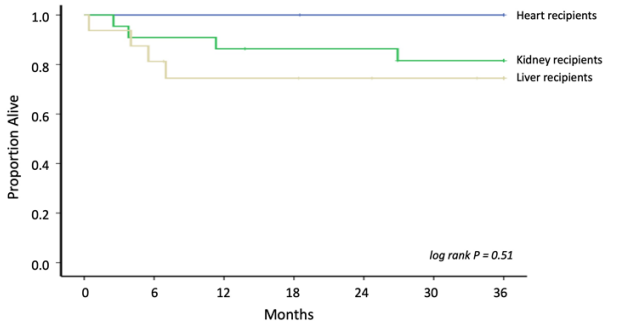

Figure 1: Kaplan Meier curve of survival after diagnosis of active tuberculosis in liver: kidney or heart transplant recipients (censored at 36 months)

Discussion

To the best of our knowledge, this is the largest report of post-SOT TB from the MENA region. Over 11 years, there were 42 cases of active TB in kidney, liver or heart transplant recipients, corresponding to an incidence rate of 1.4%. This is lower than rates reported in SOT recipients from Asian (2.4%) or African countries (3.3%) [10]. This is likely to be in part due to the higher incidence of TB in these countries compared with that in Saudi Arabia [4].

Evaluation of latent TB in potential SOT recipients is usually based on history of any known prior TB exposure, previous personal history of TB, in addition to TST or interferon gamma release assays (IGRA) [14]. A considerable proportion of the patients included in this report had documented risk factors; history of TB exposure (5, 11.9%), positive pre-transplant QFT or TST (9, 21.4%) or prior personal history of TB (5, 11.9%) (Table 1). However, only 1 patient received TB chemoprophylaxis. In a recent review of TB is SOT recipients, only 140 out of 364 cohort studies reported the risk factors for development of post-transplant TB. Of those, only 25% received TB chemoprophylaxis [10]. This represents an important missed opportunity for prevention of TB in this high-risk population and highlights the need for effective pre-transplant risk stratification and multidisciplinary discussion to decide if TB chemoprophylaxis is required and its most appropriate timing in relation to the transplant procedure. Moreover, the evaluation of transplant candidates on high-dose corticosteroid and those with history of diabetes mellitus or are living in areas with higher rates of TB should include routine chest x-rays in addition to computed tomography (CT) scans, where necessary [14,15]. Noting a higher than expected rate of post-transplant TB in our center, we implemented a policy of universal TB chemoprophylaxis for all Kidney transplant recipients with allografts from deceased donors [13].

A recent systematic review and meta-analysis compared the performance of IGRA against TST in SOT recipient. No significant difference was found in patients with clinical risk factors, prior TB or BCG vaccinations. However, the authors concluded that IGRA-based tests performed better in patients with radiological evidence of past TB [16].

Compared with renal transplant candidates, liver transplant candidates are more likely to have indeterminate QFT results [17,18]. Higher Model for End-Stage Liver Disease (MELD) scores have been shown in some studies to be associated with higher rates of indeterminate QFT results, probably due to anergy [19,20]. Thus, caution should be exercised when interpreting QFT results in SOT candidates from countries with high endemicity for TB. Additional tools such as chest imaging, history of known prior exposure should be part of the assessment. Decisions on chemoprophylaxis should be based on the overall assessment instead of one particular test or another [18,19].

The majority of our patients who were diagnosed within the first year of transplant had received induction immunosuppressive regimens. Anti-thymocyte globulin (ATG) was received by approximately one third of patients in this series. Use of lymphocyte depleting agents and/or treatment of rejection episodes were among the identified risk factors for active TB in heart transplant recipients [10]. Most (28, 66.7 %) of our patients were on tacrolimus-based regimens. In a large cohort study from India, the incidence of TB was remarkably lower in SOT recipients who received tacrolimus-based immune suppression regimens compared with cyclosporine (6.1% versus 19.9%, P <.001) [21]. In the same study, tacrolimus-based regimens were also associated with more disseminated disease. In the current study we did not evaluate the incidence of TB in both group and cannot make a conclusion on risk difference of TB between the different immunosuppressant regimens.

The majority of patients in this cohort received modified anti-tuberculous therapy. Pyrazinamide-sparing regimens were the most common modification; most often in Liver transplant patients. Fluoroquinolones were part of the first line therapy in a considerable number of patients. Current American Society of Transplantation (AST) guidelines for the treatment of TB in SOT recipients recommend that regimens similar to those used in non-transplant patients [14]. Patients who develop hepatotoxicity or impaired liver test can be treated with FQ-based therapy. Around 30% of our patients developed hepatotoxicity and underwent further modification of anti-tuberculous therapy. None of the patients developed rejection while on anti-TB therapy, including patients who were on rifampin. This may

suggest that rifampin can be used in the setting of transplantation with close monitoring of immunosuppressant levels.

Conclusion

In conclusion, post-transplant TB is relatively uncommon in SOT recipients in MENA but should be considered in the differential diagnosis in SOT recipients who present with subacute respiratory or constitutional symptoms, especially in endemic regions, or in the presence of risk factors. Risk assessment prior to transplant should include epidemiologic risk factors, results of the screening tests for latent TB and adequate radiological assessment. Caution is required when interpreting screening results. Moxifloxacin-based ATT in SOT recipients is associated with low rates of hepatotoxicity-related interruptions. Overall, clinical outcomes are acceptable, given the complexities of immune suppression and drug-drug interactions in this setting.

References

1. Black CK: Termanini KM: Aguirre O: Hawksworth JS: Sosin M (2018) Solid organ transplantation in the 21st century. Ann Transl Med 6: 409.
2. Global Observatory on Donation and Transplantation (2019) International report on organ donation and transplantation activities. Executive summary 2017.
3. Fishman JA (2017) Infection in Organ Transplantation. Am J Transplant 17: 856-879.
4. World Health Organization (2019) Global Tuberculosis Report 2019.
5. Epstein DJ: Subramanian AK (2018) Prevention and Management of Tuberculosis in Solid Organ Transplant Recipients. Infect Dis Clin North Am 32: 703-718.
6. Chen CY: Liu CJ: Feng JY (2015) Incidence and Risk Factors for Tuberculosis After Liver Transplantation in an Endemic Area: A Nationwide Population-Based Matched Cohort Study. Am J Transplant 15: 2180-2187.
7. Singh N: Paterson DL (1998) Mycobacterium tuberculosis infection in solid-organ transplant recipients: impact and implications for management. Clin Infect Dis. 27: 1266-1277.
8. Giacomelli IL: Neto RS: Nin CS (2017) High-resolution computed tomography findings of pulmonary tuberculosis in lung transplant recipients. J Bras Pneumol 43: 270-273.
9. Sparkes T: Lemonovich TL: Practice ASTIDCo. (2019) Interactions between anti-infective agents and immunosuppressants-Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice. Clin Transplant. 33: e13510.
10. Abad CLR: Razonable RR (2018) Mycobacterium tuberculosis after solid organ transplantation: A review of more than 2000 cases. Clin Transplant 32: e13259.
11. Munoz P: Rodriguez C: Bouza E (2005) Mycobacterium tuberculosis infection in recipients of solid organ transplants. Clin Infect Dis 40: 581-587.
12. Alothman A: Al Abdulkareem A: Al Hemsi B: Issa S: Al Sarraj I: et al. (2004) Isolated hepatic tuberculosis in a transplanted liver. Transpl Infect Dis 6: 84-86.
13. Al-Mukhaini SM: Al-Eid H: Alduraibi F (2017) Mycobacterium tuberculosis in solid organ transplantation: incidence before and after expanded isoniazid prophylaxis. Ann Saudi Med 37: 138-143.
14. Subramanian AK: Theodoropoulos NM (2019) Infectious Diseases Community of Practice of the American Society of Transplantation. Mycobacterium tuberculosis infections in solid organ transplantation: Guidelines from the infectious diseases community of practice of the American Society of Transplantation. Clin Transplant 33: e13513.
15. Horne DJ: Narita M: Spitters CL: Parimi S: Dodson S: et al. (2013) Challenging issues in tuberculosis in solid organ transplantation. Clin Infect Dis 57: 1473-1482.
16. Myint TM: Rogerson TE: Noble K: Craig JC: Webster AC (2019) Tests for latent tuberculosis in candidates for solid organ transplantation: A systematic review and meta-analysis. Clin Transplant 33: e13643.
17. Roth PJ: Grim SA: Gallitano S: Adams W: Clark NM: et al. (2016) Serial testing for latent tuberculosis infection in transplant candidates: a retrospective review. Transpl Infect Dis 18: 14-21.
18. Theodoropoulos N: Lanternier F: Rassiwala J (2012) Use of the QuantiFERON-TB Gold interferon-gamma release assay for screening transplant candidates: a single-center retrospective study. Transpl Infect Dis 14: 1-8.
19. Wigg AJ: Narayana SK: Anwar S (2019) High rates of indeterminate interferon-gamma release assays for the diagnosis of latent tuberculosis infection in liver transplantation candidates. Transpl Infect Dis 21: e13087.
20. Hand J: Sigel K: Huprikar S: Hamula C: Rana M (2018) Tuberculosis after liver transplantation in a large center in New York City: QuantiFERON((R)) -TB Gold-based pre-transplant screening performance and active tuberculosis post-transplant. Transpl Infect Dis 20: e12845.
21. Agarwal SK: Bhowmik D: Mahajan S: Bagchi S (2017) Impact of type of calcineurin inhibitor on post-transplant tuberculosis: Single-center study from India. Transpl Infect Dis 19.