Tuberculosis in solid-organ transplant recipients: disease characteristics and outcomes in the current era

We determined the characteristics of posttransplant tuberculosis and the impact of rifampin-based antituberculosis regimens on outcomes in the current era. Patients comprised 64 transplant recipients with tuberculosis, divided into 2 consecutive cohorts: an earlier cohort (cases occurring from 2003 to 2007) and a later cohort (cases from 2008 to 2011). Patients from the later versus earlier era had tuberculosis develop later after transplant (odds ratio, 1.01; 95% CI, 1.00-1.02; $P = .05$), were more likely to be liver transplant recipients (odds ratio, 4.52; 95% CI, 1.32-15.53; $P = .02$), and were more likely to receive tacrolimus-based immunosuppression (odds ratio, 3.24; 95% CI, 1.14-9.19; $P = .03$). Mortality rate was 10% in the later cohort and 21% in the earlier cohort ($P = .20$). Rifampin-based treatment was less likely to be used in patients with prior rejection ($P = .04$). However, neither rejection rate ($P = .71$) nor mortality ($P = .93$) after tuberculosis differed between recipients who received rifampin and recipients who did not. Thus, notable changes have occurred in the epidemiological characteristics of tuberculosis in transplant recipients. Overall mortality rate has improved, with about 90% of the patients now surviving after tuberculosis. (*Progress in Transplantation.* 2014;24:37-43)

doi: http://dx.doi.org/10.7182/pit2014398

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Tuberculosis is an important opportunistic infection in solid-organ transplant (SOT) recipients and occurs at a rate 20- to 74-fold higher in these patients than in the general population in a given geographic area.[1-5] The frequency of tuberculosis in SOT recipients ranges from 1.2% to 6.4% and may approach 15% in endemic regions.[1] Development of tuberculosis has a profound effect on outcomes in transplant recipients. Mortality rates have typically ranged from 19% to 31% and approach 44% in recipients with disseminated

tuberculosis, with 9.5% to 65% of the deaths attributable to tuberculosis.[1,4,5] The mortality rate for untreated active tuberculosis in SOT recipients is 100%.[5]

Equally relevant is the significant morbidity associated with posttransplant tuberculosis. Rejection episodes, largely due to the interactions of rifampin with immunosuppressants, have been reported in 25% to 29% of the patients with posttransplant tuberculosis.[1,2,6] In a review, graft loss due to rejection was documented in 27%.[1] Indeed, rejection following tuberculosis increased the risk of mortality by 5-fold and was an independent predictor of overall mortality in liver transplant recipients.[5] A vast majority of the reports, however, have consisted of single-center studies, had relatively small sample sizes, or comprised data published or based on cases occurring a decade or more ago.[1,7,8] The goals of this study were to determine if the epidemiological characteristics of tuberculosis in transplant recipients have evolved and to determine the impact of rifampin-based antituberculosis regimens on outcomes such as rejection, graft loss, and mortality in the current era.

Methods

Patients comprised SOT recipients diagnosed with tuberculosis at the participating sites between 2003 and 2011. For the purpose of assessing outcomes in the current era, the study population was divided into 2 consecutive (or contiguous) cohorts at the median for posttransplant tuberculosis diagnosis; one with cases occurring from 2003 to 2007 and the other from 2008 to 2011. Data generated as standard of care were collected in an observational fashion, and no study-specific interventions or procedures were employed.

Patient management and antituberculosis therapy were per standard practice at the transplant centers. Data collected included demographic characteristics, type of organ transplant, prior transplant, cytomegalovirus infection and cytomegalovirus disease as previously described,[9] rejection within 6 months before tuberculosis, renal failure at baseline (defined as serum level of creatinine ≥2 mg/dL [multiply by 88.4 to convert to micromoles per liter] at the time of diagnosis), immunosuppressive regimen at the time of diagnosis, tuberculin skin test, history of prophylaxis for latent tuberculosis infection, symptoms and signs at presentation, antituberculosis therapy, management of immunosuppressive therapy after the initiation of antituberculosis therapy, and outcomes at 12 months after the initiation of therapy.

The diagnosis of tuberculosis was based on criteria for defining tuberculosis established by the World Health Organization (smear-positive pulmonary tuberculosis, smear-negative pulmonary tuberculosis, or extrapulmonary tuberculosis).[10] Tuberculosis of an organ other than the lungs (eg, pleura, lymph nodes, abdomen, genitourinary tract, skin, joints and bones, and meninges) was considered extrapulmonary tuberculosis.[10] Involvement of 2 or more noncontiguous organ sites or of the central nervous system was regarded as disseminated tuberculosis. Approval from the institutional review board for this observational study was obtained per local requirements.

Statistical Analyses

Statistical analyses were performed by using STATA version 12.1 (Stata Corp LP). Logistic regression models were used to estimate odds ratios (ORs), 95% CIs, and *P* values. For the univariate evaluation of the type of transplant as a risk factor, the model used kidney transplant as the default group in single comparison analyses. The Fisher exact test was used to calculate *P* values when the model was unable to calculate ORs because of zero events. A multivariate model was constructed to adjust for several factors. The dependent variable was the dichotomous factor era and the predictor variables were age and those factors found to be associated with era at less than .05 level from the univariate logistic models. The standard errors in the multivariate model were adjusted by clustering on site (institution), that is, we controlled for any differences in sites. The final model was evaluated by using the Hosmer-Lemeshow goodness-of-fit test. Univariate logistic models were used to evaluate factors associated with receipt of rifampin.

Results

Of 64 consecutive SOT recipients with tuberculosis, 34 (53%) had received a kidney, 19 (30%) a liver, 7 (11%) a heart, 3 (5%) a lung, and 1 (2%) a kidney-pancreas transplant (Table 1). None of the patients were positive for human immunodeficiency virus. Of study patients, 3 (5%) were retransplant recipients; all others were primary transplant recipients. The diagnosis of tuberculosis was established by culture in 80% (51/64) of the patients, histopathologic examination in 8% (5/64), clinical criteria and response to therapy in 8% (5/64), and by acid-fast smear in 5% (3/64). Overall, 58% (37/64) of the patients had pulmonary disease only and 42% (27/64) had both pulmonary and extrapulmonary tuberculosis. Disseminated tuberculosis occurred in 16% (10/64) of the patients; these included 7 kidney and 3 liver transplant recipients. Central nervous system disease was present in only 2 patients; both were liver transplant recipients.

Tuberculosis developed a median of 12 months after transplant (interquartile range [IQR], 5-58 months), with 50% (32/64) of the cases occurring after the first posttransplant year. The median time to onset was 33 months in the later cohort versus 8 months after transplant in the early cohort ($P = .04$). Median time to onset of tuberculosis did not differ significantly

Table 1 Demographic and clinical characteristics of the patients (N = 64)

Variable	Value[a]
Age, median (IQR), y	55 (43-66)
Sex	
Male	40 (62)
Female	23 (36)
Unknown	1 (2)
Type of transplant	
Kidney	34 (53)
Liver	19 (30)
Heart	7 (11)
Lung	3 (5)
Kidney-pancreas	1 (2)
Living donor[b]	9 (14)
Prior retransplant	3 (5)
CMV infection	13/60 (22)[c]
CMV disease	7/60 (12)
Renal dysfunction (creatinine[d] ≥2mg/dL)	22 (34)
Dialysis	7 (11)
Prior allograft rejection	7 (11)
Baseline immunosuppression	
Any calcineurin inhibitor	46 (72)
Tacrolimus	26 (41)
Cyclosporine A	20 (31)
Sirolimus	5 (8)
Azathioprine	3 (5)
Mycophenolate mofetil	35 (55)
Prednisone	53 (83)
Dose, median (IQR), mg	5 (5-10)
Anti-T cell agent	12 (19)
Characteristics of tuberculosis	
Prior tuberculin testing	24 (38)
Tuberculin reactivity[e]	8
Time to onset of tuberculosis, median (IQR), months	12 (5-58)
Type of disease	
Pulmonary (only)	37 (58)
Pulmonary (any)	54 (84)
Extrapulmonary	27 (42)
Disseminated	10 (16)

Abbreviations: CMV, cytomegalovirus; IQR, interquartile range.

[a] Values are number (percentage) unless otherwise indicated.

[b] Living donors were all kidney transplants.

[c] CMV infection and disease history were not available for 4 patients.

[d] Multiply by 88.4 to convert to micromoles per liter.

[e] Only 1 patient had received prior treatment for tuberculin reactivity.

between pulmonary (17 months; IQR, 5-53 months), extrapulmonary (15 months; IQR, 6-53 months, $P = .69$), or disseminated tuberculosis (17 months; IQR, 4-32 months; $P = .59$).

Comparison of Patients in the 2 Eras

Overall, 33 (52%) of the 64 cases occurred between 2003 and 2007 and 31 (48%) between 2008 and 2012. The 2 cohorts did not differ significantly with regards to age, prior CMV infection, renal dysfunction, dialysis, retransplant, clinical manifestations (fever, weight loss, night sweats, cough, malaise), site of involvement (pulmonary, extrapulmonary, or disseminated), rejection before tuberculosis, and changes in immunosuppression at diagnosis (Table 2). However, patients in the later compared with the earlier era were more likely to be older ($P = .08$), to be liver transplant recipients ($P = .02$), to receive tacrolimus-based immunosuppression ($P = .03$), and to have tuberculosis develop later after transplant ($P = .04$). In a multivariate model (adjusted for cluster in site), liver transplant (OR, 3.9; 95% CI, 1.05-14.56, $P = .04$), tacrolimus use (OR, 3.5; 95% CI, 1.76-6.95; $P < .001$), and time to onset (OR, 1.01; 95% CI, 1.00-1.02; $P = .049$) were independently associated with the time period (Table 3). The goodness-of-fit test indicated that the model was adequate and the observed and expected events for the model subgroups did not differ significantly ($P = .32$).

Comparison between the 2 cohorts showed that the rate of cytomegalovirus infection ($P = .36$), the timing of cytomegalovirus infection ($P = .99$), and the receipt of prophylaxis for latent tuberculosis before transplant ($P = .36$) did not differ significantly between liver transplant recipients and recipients of other types of transplants (Table 4). The number and proportion of patients who were liver transplant recipients also did not change significantly from the early to the late era (Table 4). However, liver transplant recipients in the early era were less likely to have received triple-drug immunosuppression (calcineurin-inhibitor agent, antimetabolite, and prednisone) than were recipients of other transplants ($P = .04$), whereas no such difference between the groups was apparent in the second era ($P = .80$); these data were adjusted for cluster in site. None of the cases occurred in the setting of an outbreak.

Outcomes

Overall mortality at 12 months was 16% (10/64). The causes of death were superimposed pneumonia, candidemia, and urosepsis in 3 kidney transplant recipients; sepsis, recurrence of hepatitis C, and gastrointestinal bleeding in 4 liver transplant recipients; graft failure and sepsis in 1 lung transplant recipient, and sepsis in 1 heart transplant recipient. Only 1 death (in a kidney transplant recipient) was deemed attributable to tuberculosis by the investigator. Mortality rate was 10% in the later cohort versus 21% in the earlier cohort ($P = .20$).

Excluding 1 patient who died before treatment was initiated, 63 patients received antituberculosis therapy. Of these, 94% (59/63) received at least a 3-drug antituberculous regimen. Rifampin-based treatment was used in 41% (26/63) of the patients. Patients receiving rifampin did not differ from those treated with a regimen not based on rifampin with respect to age,

Table 2 Changes in immunosuppression at diagnosis of tuberculosis

	Percentage (proportion) of patients		
Change	Later era	Earlier era	Odds ratio (95%CI), *P*
Discontinuation of CNI	14 (3/22)	4 (1/24)	3.79 (0.36-39.41), .30
Any reduction in CNI	36 (8/22)	12 (3/24)	2.86 (0.72-11.37), .11
≥50% reduction in CNI	27 (6/22)	8 (2/24)	4.31 (0.77-24.15), .14
Discontinuation of prednisone	10 (1/10)	6 (1/18)	1.89 (0.11-33.89), .67
Any reduction in prednisone	50 (5/10)	33 (6/18)	2.00 (0.41-9.71), .39
≥50% reduction in prednisone	20 (2/10)	17 (3/18)	1.25 (0.17-9.09), .83
Discontinuation of AZA/MMF	6 (1/18)	4 (1/23)	1.29 (0.8-22.22), .86
Discontinuation of all agents	0	0	0

Abbreviations: AZA, azathioprine; CNI, calcineurin-inhibitor agent; MMF, mycophenolate mofetil.

type of transplant, time to onset of tuberculosis after transplant, prior cytomegalovirus infection, renal failure, requirement of dialysis, extrapulmonary or disseminated disease, and clinical manifestations (Table 5). Rifampin was significantly less likely to be used in patients with prior rejection (0/7 vs 23/56, $P = .04$) than in patients without rejection. However, neither rejection rate (8% vs 5%, $P = .72$) nor mortality (15% vs 16%, $P = .93$) after the diagnosis of tuberculosis differed significantly between rifampin recipients and nonrifampin recipients (Table 5). Dose of calcineurin-inhibitor agent was increased in 79% of the patients who received rifampin.

Discussion

Several observations can be made about our study results with regard to posttransplant tuberculosis in the current era. Certain characteristics of the disease have remained unchanged. For example, 42% of our patients had extrapulmonary tuberculosis and 16% had disseminated disease. These percentages are similar to the 16% to 67% rate of extrapulmonary tuberculosis[1,3,5] and the 10% to 33% rate of disseminated tuberculosis in SOT recipients in previous reports[3-5] and did not differ significantly for the 2 cohorts in this study (Table 3).

Other characteristics of the disease, however, have evolved. Patients in the current era were more likely to receive tacrolimus-based immunosuppression, to have tuberculosis develop later in the posttransplant period, and to be liver transplant recipients. Although approximately 70% of the patients in both cohorts received calcineurin-inhibitor agent, the use of tacrolimus tended to be greater and that of cyclosporine to be less in the later era than in the earlier era. These changes reflect current practices, where tacrolimus has emerged as the primary immunosuppressant used in transplant recipients.[11]

Whereas most cases of tuberculosis in SOT recipients (63%-95% of the cases) in the past have occurred within the first posttransplant year,[1,4] patients in the current era were significantly more likely to have tuberculosis develop later in the posttransplant period (Table 3). These observations may be due to delayed occurrence of risk factors, for example, older age of the recipients (Table 3) or later onset of cytomegalovirus infection. It is also plausible that other factors portending a risk for tuberculosis that were not assessed in this study (eg, delayed onset of recurrence of hepatitis C) may also have contributed to these trends.[12] We note that a trend toward delayed occurrence does not appear to be unique to tuberculosis but has been reported with other opportunistic infections in SOT recipients.[13] Finally, the proportionately higher number of cases of tuberculosis that were liver transplants in the current era appears to be due to increased use of triple-agent immunosuppression in these patients in the later period.

Mortality rates in SOT recipients in recent studies have ranged from 13% to 19%.[4,7] Overall mortality rate in our study was 16%. When stratified by the cohort, the mortality rate was 10% in the later cohort and 21% in the earlier cohort. In a meta-analysis, employment of 3 or more antituberculosis drugs was independently associated with lower mortality (OR, 0.01; 95% CI, 0.02-0.6) and posttuberculosis rejection (OR, 5.0; 95% CI, 1.2-20) (but not pretuberculosis rejection) was associated with higher mortality.[5] Overall, 94% of our patients received at least 3 drugs in their antituberculosis regimen, and this did not differ for the 2 cohorts. Notably however, only 43% of the patients received a rifampin-based regimen. These data are in contrast with previous reports where rifampin was used in 81% to 100% of the patients.[4,7,14] Patients with pretuberculosis rejection were significantly less likely to receive a rifampin-based regimen. The posttuberculosis rejection rate and mortality rate did not differ significantly between patients who did and did not receive rifampin-based regimens. Whether these findings are due to deliberate selection of patients receiving rifampin

Table 3 Comparison of 2 cohorts of transplant recipients with tuberculosis (TB)

Factor	Odds of TB occurring in later (2008-2012) vs earlier (2003-2007) cohort [95%CI]	Comparison (reference) group	*P*	Multivariate model, odds ratio [95% CI], *P*
Type of transplant				
Liver	4.52 [1.32-15.53]	Kidney transplant	.02	3.9 [1.05-14.56], .04
Lung	0.81 [0.07-9.82]		.87	
Heart	0.65 [0.11-3.83]		.63	
Kidney-pancreas	Unable to calculate[a]		.99	
CMV infection	0.71 [0.20-2.49]	No CMV infection	.59	
CMV disease	0.45 [0.08-2.52]	No CMV disease	.36	
Creatinine level[b] ≥2 mg/dL	0.83 [0.29-2.34]	Creatinine <2 mg/dL	.73	
Dialysis	2.98 [0.53-16.66]	No dialysis	.21	
Rejection before tuberculosis	3.37 [0.60-18.93]	No prior rejection	.17	
Age	1.03 [1.00-1.06]	Continuous	.08	1.01 [0.95-1.07], .73
Male sex	0.99 [0.35-2.75]	Female	.98	
Immunosuppression				
Any CNI	0.92 [0.31-2.73]	No CNI	.88	3.49 [1.76-6.95], <.001
Tacrolimus	3.24 [1.14-9.19]	No tacrolimus	.03	
Cyclosporine A	0.23 [0.07-0.75]	No cyclosporine A	.02	
Prednisone	0.35 [0.08-1.52]	No prednisone	.16	
Sirolimus	0.69 [0.11-4.43]	No sirolimus	.70	
AZA	2.21 [0.19-25.64]	No azathioprine	.53	
MMF	0.36 [0.13-1.00]	No MMF	.05	
Triple-agent immunosuppression (CNI, AZA/MMF, and prednisone)	0.47 [0.16-1.36]	No triple immunosuppression	.16	
Time to development of TB after transplant	1.01 [1.00-1.02]	Continuous	.04	1.01 [1.00-1.02], .049
Clinical manifestations				
Fever	0.93 [0.34-2.55]	No fever	.89	
Weight loss	1.18 [0.38-3.63]	No weight loss	.78	
Malaise	0.64 [0.23-1.79]	No malaise	.40	
Night sweats	1.08 [0.28-4.15]	No night sweats	.91	
Cough	0.61 [0.21-1.78]	No cough	.36	
Time from onset of symptoms to diagnosis	1.00 [0.99-1.01]	Continuous	.18	
Sites of TB				
Pulmonary (any)	1.5 [0.38-5.92]	No pulmonary TB	.56	
Extrapulmonary	0.58 [0.21-1.59]	No extrapulmonary TB	.29	
Disseminated	1.07 [0.28-4.15]	No dissemination	.91	
Treatment of TB				
Isoniazid	3.10 [0.30-31.58]	No isoniazid	.34	
Rifampin	0.81 [0.30-2.22]	No rifampin	.68	
Ethambutol	1.50 [0.23-9.65]	No ethambutol	.66	
Pyrazinamide	1.97 [0.67-5.76]	No pyrazinamide	.22	
Quinolone	0.79 [0.29-2.16]	No quinolone	.65	
≥3 anti-TB drugs	3.10 [0.30-31.58]	<3 drugs	.34	
Outcomes at 12 months				
Rejection	0.33 [0.03-3.39]	No post-TB rejection	.35	
Graft loss	Unable to calculate[a]	No graft loss	.99	
Mortality	0.39 [0.09-1.70]	No mortality	.21	

Abbreviations: AZA, azathioprine; CMV, cytomegalovirus; CNI, calcineurin inhibitor; MMF, mycophenolate mofetil.

[a] No patients were in the comparator group with the event, and therefore odds ratio could not be calculated.

[b] Multiply by 88.4 to convert to micromoles per liter.

(with avoidance in those with prior rejection), overall lower risk of rejection in the late posttransplant period when most cases of tuberculosis occurred, or availability of alternative options for treatment such as quinolones is not entirely known but remains plausible.

Table 4 Percentages of each type of organ transplant in each era

Type of transplant	No. of transplants between 2003 and 2007	Percentage[a]	No. of transplants between 2008 and 2011	Percentage[a]
Kidney	3041	56.3	2820	54.8
Kidney-pancreas	164	3.0	268	5.2
Liver	1502	27.8	1352	26.3
Heart	491	9.1	479	9.3
Lung	205	3.8	228	4.4
Total	5403	100	5147	100

[a] Percentages represent the number of specific type of transplant divided by total number of transplants in that era. Percentages did not change significantly between the eras.

Table 5 Comparison of patients who did and did not receive rifampin-based regimen

Factor	Odds of patients receiving rifampin-based regimen [95%CI]	Comparison (reference) group	*P*
Age	1.00 [0.97-1.03]	Continuous	.87
Male sex	0.54 [0.19-1.55]	Female	.25
Type of transplant			
Liver	1.02 [0.32-3.29]	Kidney transplant	.97
Heart	2.33 [0.44-12.22]		.32
Lung	3.50 [0.29-42.74]		.33
Kidney-pancreas	Unable to calculate[a]		.99
Time to onset of TB after transplant	1.00 [0.99-1.01]	Continuous	.58
Retransplant	Unable to calculate[b]	Initial transplant	.26
Prior rejection	Unable to calculate[c]	No prior rejection	.04
CMV infection	0.53 [0.14-1.97]	No CMV infection	.34
CMV disease	0.19 [0.02-1.73]	No CMV disease	.14
Creatinine level[d] ≥2 mg/dL	0.61 [0.20-1.80]	Creatinine <2 mg/dL	.37
Dialysis	0.21 [0.02-1.83]	No dialysis	.16
Prior tuberculin test done	0.43 [0.14-1.31]	Tuberculin not done	.14
Tuberculin positive	1.80 [0.29-11.16]	Tuberculin negative	.53
Extrapulmonary TB	1.26 [0.46-3.46]	No extrapulmonary	.66
Disseminated TB	0.56 [0.13-2.40]	No dissemination	.43
Signs and symptoms			
Fever	1.47 [0.51-4.24]	No fever	.47
Weight loss	1.14 [0.36-3.59]	No weight loss	.83
Malaise	0.43 [0.15-1.28]	No malaise	.13
Night sweats	0.30 [0.06-1.56]	No night sweats	.15
Outcomes at 12 months			
Rejection	1.46 [0.19-11.08]	No post-TB rejection	.72
Mortality	0.94 [0.24-3.72]	Alive at 1 year	.93

Abbreviations: CMV, cytomegalovirus; TB, tuberculosis.
[a] One of 1 kidney-pancreas transplant.
[b] Zero of 3 retransplants.
[c] Zero of 7 with prior rejection received rifampin.
[d] Multiply by 88.4 to convert to micromoles per liter.

Several limitations of our study deserve to be acknowledged. Although our case definitions comprised the World Health Association's proposed criteria for tuberculosis, it is possible that some patients with a diagnosis of tuberculosis that was not based on culture did not have tuberculosis. However, this possibility is

unlikely because all patients received therapy specifically against tuberculosis with resolution of clinical manifestations. Our study was based on data collected as standard of practice and was not designed to assess the effectiveness of a particular regimen. Strengths of our study include the fact that our sample size is among the largest in SOT recipients with tuberculosis, data were systematically collected by using a uniform data collection tool, and this study involved multiple centers, which renders our findings generalizable.

Summary

Our data show that noteworthy changes have occurred in the epidemiological characteristics and outcomes in SOT recipients with tuberculosis. These include most notably later onset of tuberculosis in the current era. Overall, mortality rates appear to have improved, with nearly 90% of the transplant recipients surviving 12 months after the development of tuberculosis. Rifampin-based regimens, although used in only 43% of the patients in the current era, did not appear to be associated with posttuberculosis rejection or mortality.

Financial Disclosures

The Spanish investigators are supported by Ministerio de Economía y Competitividad, Instituto de Salud Carlos III, cofinanced by European Development Regional Fund "A way to achieve Europe" ERDF, and Spanish Network for the Research in Infectious Diseases (REIPI RD06/0008 and RD12/0015). Ana Garcia-Reyne was supported by a grant from Instituto de Salud Carlos III (Río Hortega, Grant # CN09130).

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