Mycobacterium Tuberculosis—Associated Immune Reconstitution Syndrome in Solid-Organ Transplant Recipients

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Background. Incidence, characteristics, and risk factors for tuberculosis (TB)-associated immune reconstitution inflammatory syndrome (IRS) in solid-organ transplant (SOT) recipients are not known.
Methods. Patients are composed of 64 consecutive SOT recipients with TB followed for 12 months. IRS was defined based on previously proposed criteria.
Results. IRS developed in 14% (9/64) of the patients, a median of 47 days after the use of anti-TB therapy. Liver versus other types of organ transplant recipients (adjusted odds ratio [OR], 6.11; 95% confidence interval [CI], 1.08–34.86), prior cytomegalovirus infection (adjusted OR, 5.65; 95% CI, 0.93–34.47), and rifampin use (adjusted OR, 4.56; 95% CI, 0.74–27) were associated with a higher risk of IRS. The presence of more than one factor (liver transplantation, cytomegalovirus infection, and rifampin use) when compared with none of these factors conferred a 19-fold increase in the risk of IRS (P=0.01). Mortality at 1 year after diagnosis was 33.3% in patients with IRS and 17.2% in those without IRS (P=0.31).
Conclusions. IRS was documented in 14% of the SOT recipients with TB. We determined clinically identifiable factors that may be useful in assessing the risk of tuberculosis-associated posttransplantation IRS.

Keywords: Immune reconstitution syndrome, Mycobacterium tuberculosis, Solid-organ transplant recipients.

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Mycobacterium tuberculosis is a significant opportunistic pathogen in solid-organ transplant (SOT) recipients. The incidence of tuberculosis (TB) in SOT recipients ranges from 1.2% to 6.4% and is 20 to 74 times higher than that in the general population in a given geographic area (*1–3*). Nearly one-half of the transplant recipients with TB have extrapulmonary or disseminated infection. The overall mortality rate in SOT recipients with TB is as high as 29% (*1*).

Cell-mediated immunity, particularly activated macrophages, T cells, and type 1 cytokines, play a pivotal role in controlling mycobacterial infection (*4, 5*). M. tuberculosis induces not only proinflammatory cytokines, such as interleukin (IL)-2, IL-1, and tumor necrosis factor, which are essential for host resistance (*6*) but also anti-inflammatory cytokines, including IL-10 and transforming growth factor β that downregulate proinflammatory responses and T-cell proliferation/activation. Progressive impairment in

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M. tuberculosis–specific T-cell response with increasing mycobacterial load recovered with therapy (*7*). M. tuberculosis–associated immunocompromised state is potentially reversible on initiation of antimycobacterial therapy and concurrent attempts at restoring immunity, such as the use of antiretroviral therapy (ART) in human immunodeficiency virus (HIV)-positive patients.

Immune reconstitution inflammatory syndrome (IRS) is a state of heightened and dysregulated inflammatory response to invading microorganisms (*8, 9*). The proposed basis of IRS is a shift of host immunity from an anti-inflammatory and immunosuppressive status toward a pathogenic inflammatory state as a result of decrease or removal of factors promoting immunosuppression or inhibiting inflammation. Granulomatous infections, such as opportunistic mycoses and mycobacterial disease, are most commonly associated with IRS (*10, 11*). TB-associated IRS occurs in 8% to 43% of the HIV-infected patients typically within 3 months after ART is initiated.

Anecdotal reports suggest that IRS may also be observed in SOT recipients with TB (*12, 13*). However, no studies to date have systematically assessed TB-associated IRS in this host population. Thus, this study aimed to assess the incidence, characteristics, risk factors, and outcomes for IRS in SOT recipients with TB.

RESULTS

Patients are composed of 64 consecutive SOT recipients with TB followed for 12 months. Overall, 34 (53%) were kidney transplant recipients; 19 (30%), liver transplant recipients; 7 (11%), heart transplant recipients; 3 (4.6%), lung transplant recipients; and 1 (1.7%) kidney-pancreas transplant recipient. None of the patients were HIV positive. Primary immunosuppressive regimen was calcineurin inhibitor (CNI) based in 46 (72%) of the patients, including tacrolimus in 26 (41%) and cyclosporine in 20 (31%). In all, 83% of the patients were receiving prednisone at diagnosis (median dose, 5 mg). The onset of TB was a median of 12 months after transplantation (interquartile range, 5–58.1 months). TB was diagnosed by culture in 80% (51/64) of the transplant recipients, by acid-fast smear in 5% (3/64), histopathology in 8% (5/64), and clinical criteria and response to therapy in 8% (5/64). Overall, 58% (37/64) had pulmonary and 42% (27/64) had extrapulmonary TB. Central nervous system (CNS) disease was present in only two patients.

Characteristics of Patients with IRS

Of the 64 transplant recipients with TB, 9 (14.1%) developed IRS, of which 6 are liver transplant recipients, 2 are renal transplant recipients, and 1 is a heart transplant recipient. Detailed information of the patients with IRS is outlined in Table 1. IRS developed a median of 47 days (interquartile range, 12–77 days) after initiation of anti-TB therapy; all but one case occurred within 100 days of initiation of therapy. Sites of involvement at the diagnosis of TB were pulmonary in four, pulmonary and pleural in two, CNS in one, pulmonary and CNS in one, and miliary in one case. All cases were culture positive for M. tuberculosis at baseline except for one who was diagnosed based on histopathology. IRS manifested as new onset or worsening pleural effusion in three, worsening pulmonary lesions in two, new-onset pericardial effusion in one, unexplained fever in one, new-onset lymphadenopathy in one, and CNS tuberculoma with hydrocephalus in one patient (Table 1). Diagnostic workup did not reveal active TB (all cases were culture negative at the time of IRS), and anti-TB regimen was not changed in any of the patients with IRS (Table 1).

Risk Factors for IRS

The comparison of SOT recipients with TB and IRS and those without IRS is shown in Table 2. Age, gender, time to onset of TB, renal failure at baseline, prior rejection, and use of CNI or T-cell–depleting agents did not correlate with IRS. Discontinuation of CNI, any reduction of CNI, more than 50% reduction of CNI, discontinuation of prednisone, any reduction of prednisone, more than 50% reduction of prednisone, discontinuation of azathioprine/mycophenolate mofetil, and discontinuation of all immunosuppressant agents were not associated with the development of IRS (Table 2). In addition, extrapulmonary TB, culture positivity, isolates with isoniazid or rifampin resistance, and post-TB rejection were not associated with the development of IRS (Table 2).

Compared with SOT recipients without IRS, cases with IRS were more likely to be liver transplant recipients (odds ratio [OR], 6.5; 95% confidence interval [CI], 1.41–29.5; P=0.016), to have prior cytomegalovirus (CMV) infection (OR, 4.78; 95% CI, 1.00–22.76; P=0.05), to have TB with CNS involvement (22.2% vs. 0%, P=0.01), to have received rifampin-based anti-TB regimen (OR, 3.40; 95% CI, 0.76–15.11; P=0.10), and less likely to have received prednisone at baseline as immunosuppressant (OR, 0.146; 95% CI, 0.03–0.75; P=0.020) (Table 2).

Logistic regression analyses were performed to determine the variables that predicted the risk of IRS. Factors considered for inclusion in the model were those that were statistically significance (P<0.10) or those considered to be clinically relevant (Tables 3 and 4). Although CNS involvement and prednisone use at baseline were significantly associated with IRS in univariate analysis, these variables were highly correlated with liver transplantation. Nine of 10 patients without prednisone use were liver transplant recipients. In addition, only 2 of 64 patients had CNS disease, and both were liver transplant recipients. The multivariate model therefore included liver transplantation, CMV infection, and rifampin use. Table 3 depicts the results of the logistic model and the classification functions for these variables. Liver transplantation was independently associated with IRS (adjusted OR, 6.11; 95% CI, 1.08–34.86; P=0.04). The risk with CMV infection (adjusted OR, 5.65; 95% CI, 0.93–34.47; P=0.06) and rifampin use (adjusted OR, 4.56; 95% CI, 0.74–27.95; P=0.10) are depicted in Table 3. IRS occurred in 5% (1/20) of the subjects with none of the aforementioned factors, 6.2% (2/32) with one, 40% (4/10) with two, and 2/2 subjects with all three factors present (χ^2 for trend P=0.003).

Extrapulmonary disease has been associated with IRS in other hosts with TB (*14, 15*) and has been shown to be a clinically important factor influencing outcomes in TB (*16, 17*). An additional model was therefore constructed to evaluate the effect of liver transplantation, CMV infection, and extrapulmonary TB on the occurrence of IRS (Table 4).

TABLE 1. Detailed information of solid-organ transplant recipients with immune reconstitution syndrome

Patient	Transplantation Type	Onset of TB After Transplantation	Interval Between Anti-TB Initiation to IRS, d	Site of Initial TB/Anti-TB Therapy	Methods of TB Diagnosis	Symptoms/Site IRS	Management After IRS	Outcome
1	Liver	6 y	77	Pulmonary/INH/RIF/EMB	Culture based	New-onset fever with constitutional symptoms	Sputum AFB and culture negative for Mycobacterium tuberculosis; no change in anti-TB regimen	Alive
2	Liver	18 d	467	Meningitis/INH/PZA/EMB	Culture based	Tuberculoma/hydrocephalus	CSF AFB and culture negative for M. tuberculosis	Alive
3	Liver	9 d	47	Pulmonary INH/EMB/PZA/levofloxacin	Culture based	Pleural effusion	Pleural fluid AFB and culture negative for M. tuberculosis; no change in anti-TB regimen	Died because of HCV recurrence
4	Kidney	4 y	12	Pulmonary INH/RIF/EMB/PZA	Culture based	Pericardial effusion	No change in anti-TB regimen	Died because of candidemia
5	Liver	4 mo	8	Pulmonary/CNS/INH/RIF/EMB/levofloxacin	Culture based	Fever, increased pleural effusion, mental status changes	CSF AFB and culture negative for M. tuberculosis; no change in anti-TB regimen	Died because of septic shock
6	Kidney	7 mo	7	Pulmonary/INH/EMB/levofloxacin	Culture based	Hemoptysis/worsening CXR	Sputum AFB positive, but culture negative for M. tuberculosis; no change in anti-TB regimen	Alive
7	Liver	5 y	59	Pulmonary/pleural/INH/RIF/EMB/PZA	Culture based	Increased pleural effusion	Pleural effusion AFB and culture negative for M. tuberculosis; no change in anti-TB regimen	Alive
8	Heart	2.4 mo	99	Pulmonary/pleural/INH/RIF/EMB/PZA	Culture based	New cervical lymphadenopathy	Lymph node AFB negative, culture negative for M. tuberculosis; no change in anti-TB regimen	Alive
9	Liver	13 y	27	Pulmonary/miliary INH/rifabutin/EMB/PZA	Histopathology	Worsening radiographic findings	Sputum AFB smear positive, but culture negative for M. tuberculosis; no change in anti-TB regimen	Alive

Patient 2 developed IRS 103 days after completion of 12-month course of therapy.

AFB, acid-fast bacilli; CNS, central nervous system; CSF, cerebrospinal fluid; EMB, ethambutol; HCV, hepatitis C virus; INH, isoniazid; IRS, immune reconstitution syndrome; PZA, pyrazinamide; RIF, rifampin; TB, tuberculosis.

TABLE 2. Demographics and clinical characteristics of solid-organ transplant recipients with and without tuberculosis-associated immune reconstitution syndrome

Factor	IRS (n=9)	No IRS (n=55)	Odds of IRS with factor, OR (95% CI)	*P*
Demographic data				
Age, median (IQR), y	60 (47–64)	55 (43–67)	1.005 (0.96–1.05)	0.83
Gender, % (n)				
Female	44.4 (4/6)	34.0 (18/53)	(Odds if male)	
Male	55.6 (5/9)	66.0 (35/53)	0.643 (0.15–2.69)	0.54
Transplant, % (n)				
Liver	66.7 (6/9)	23.6 (13/55)	6.5 (1.41–29.5)	0.016 (liver vs. all others)
Lung	(0/9)	5.4 (3/55)	(Odds if liver)	
Kidney	22.2 (2/9)	58.2 (32/55)		
Heart	11.1 (1/9)	10.9 (6/55)		
Kidney-pancreas	(0/9)	1.8 (1/55)		
Living donor, % (n)	(0/9)	16.4 (9/55)	Unable to calculate[a]	
Other clinical data				
Prior transplantation, % (n)	(0/9)	4.5 (3/55)	Unable to calculate[a]	0.47
CMV infection, % (n)	50 (4/8)	17.3 (9/52)	4.78 (1.00–22.76)	0.05
CMV disease, % (n)	14.3 (1/7)	11.3 (6/53)	1.30 (0.13–12.8)	0.81
Creatinine, ≥2 mg/dL, % (n)	22.2 (2/9)	36.4 (20/55)	0.50 (0.09–2.64)	0.41
Dialysis	(0/9)	12.7 (7/55)	Unable to calculate[a]	0.25
Positive tuberculin skin test, % (n)	25 (2/8)	42.3 (22/52)	0.45 (0.08–2.47)	0.36
TB prophylaxis, % (n)	(0/9)	3.7 (2/54)	Unable to calculate[a]	0.55
Prior TB, % (n)	11.1 (1/9)	9.3 (5/54)	1.22 (0.13–11.89)	0.86
Timing of TB after transplantation, median (IQR), mo	8 (2–66)	13 (6–51)	1.00 (0.99–1.01)	0.91
Prior rejection, % (n)	(0/8)	13.2 (7/53)	Unable to calculate[a]	0.27
Baseline immunosuppression, % (n)				
Tacrolimus	44.4 (4/9)	40.0 (22/55)	1.20 (0.29–4.97)	0.80
Cyclosporine A	33.3 (3/9)	30.9 (17/55)	1.12 (0.25–5.01)	0.88
Any CNI	77.8 (7/9)	70.9 (39/55)	1.43 (0.27–7.67)	0.67
Sirolimus	22.2 (2/9)	16.4 (9/55)	1.46 (0.26–8.21)	0.66
Azathioprine	(0/9)	5.45 (3/55)	Unable to calculate[a]	0.47
Mycophenolate mofetil	33.3 (3/9)	58.2 (32/55)	0.359 (0.08–1.59)	0.17
Prednisone	55.6 (5/9)	88.9 (48/54)	0.146 (0.03–0.75)	0.02
Anti–T-cell agents	11.1 (1/9)	20.0 (11/55)	0.500 (0.05–4.42)	0.53
Triple therapy (CNI+MMF+prednisone)	11.1 (1/9)	30.9 (17/55)	0.279 (0.03–2.41)	0.24
Change in immunosuppression at diagnosis of TB, % (n)				
Discontinuation of CNI	(0/7)	7.7 (3/39)	Unable to calculate[a]	0.52
Any reduction of CNI	28.6 (2/7)	15.4 (6/39)	2.20 (0.34–14.08)	0.40

≥50% reduction of CNI	14.3 (1/7)	10.3 (4/39)	1.45 (0.14–15.39)	0.75
Discontinuation of prednisone	(0/5)	4.2 (2/48)	Unable to calculate[a]	0.64
Any reduction of prednisone	20 (1/5)	16.7 (8/48)	1.25 (0.12–12.71)	0.85
≥50% reduction of prednisone	20 (1/5)	12.5 (6/48)	12.5 (6/48)	0.64
Discontinuation of Aza/MMF	(0/3)	5.3 (2/38)	Unable to calculate[a]	0.68
Discontinuation of all agents	(0/9)	3.6 (2/55)	Unable to calculate[a]	0.56
Posttuberculosis rejection	11.1 (1/9)	5.45 (3/55)	2.17 (0.20–23.47)	0.52
TB characteristics				
Extrapulmonary TB, % (n)	66.7 (6/9)	38.2 (21/55)	3.24 (0.73–14.35)	0.12
CNS TB, % (n)	22.2 (2/9)	(0/55)	Unable to calculate[a]	0.01
Culture positive, % (n)	77.8 (7/9)	80.0 (44/55)	0.875 (0.16–4.81)	0.87
Duration of anti-TB therapy, mo	9 (6–12)	11 (9–12)	0.90 (0.77–1.06)	0.25
Patients who received rifampin[b], % (n)	66.7 (6/9)	37.0 (20/54)	3.40 (0.76–15.11)	0.10
CNI increase	75 (3/4)	70.0 (7/10)	1.28 (0.06–89.7)	0.852
No change in CNI	25 (1/4)	20.0 (2/10)	1.16 (0.02–31.67)	0.913
Prednisone increase	0 (0/1)	0 (0/6)	Unable to calculate[a]	—
No change in prednisone	100 (1/1)	83.3 (5/6)	Unable to calculate[a]	0.857
Patients who did not receive rifampin[b]				
CNI increase	0 (0/2)	21.4 (4/16)	Unable to calculate[a]	0.471
No change in CNI	50 (1/2)	47.4 (9/19)	1.11 (0.01–95.8)	0.943
Prednisone increase	0 (0/3)	13.3 (2/15)	Unable to calculate[a]	0.502
No change in prednisone	0 (0/3)	40.0 (6/15)	Unable to calculate[a]	0.269
Isoniazid resistance[c]	14.3 (1/7)	5.3 (2/38)	3.0 (0.23–38.5)	0.39
Rifampin resistance[c]	14.3 (1/7)	0 (0/38)	Unable to calculate[c]	0.15
Change in immunosuppression at time of CMV infection, % (n)				
Number with reduction in immunosuppression	75 (3/4)	22.2 (2/9)	3.0 (0.31–28.8)[d]	0.21

[a] We were unable to calculate odds ratio given zero value in one of the comparator that yields infinite odds.
[b] Data depict change in immunosuppression from baseline to 4 weeks.
[c] Data refer to the resistance at diagnosis of tuberculosis.
[d] Value represents the odds of IRS with reduction in immunosuppression for CMV infection.

Aza, azathioprine; CI, confidence interval; CMV, cytomegalovirus; CNI, calcineurin inhibitors; CNS, central nervous system; IQR, interquartile range; IRS, immune reconstitution syndrome; MMF, mycophenolate mofetil; OR, odds ratio; TB, tuberculosis.

TABLE 3. Multivariate analysis of factors associated with immune reconstitution syndrome (Model 1)

Factor	Reference Group	Adjusted OR (95% CI)	*P*
Liver transplantation	No liver transplantation	6.11 (1.08–34.86)	0.04
Rifampin use	No rifampin use	4.56 (0.74–27.95)	0.10
CMV infection	No CMV infection	5.65 (0.93–34.47)	0.06
Risk prediction of IRS			
One of the above factors present	None of the above factors present	11.26 (0.11–14.95)	0.85
More than one of the above factors present	None of the above factors present	19.00 (1.89–190.92)	0.01
Diagnostic accuracy and estimates of probability of IRS using liver transplantation, rifampin use, and CMV infection in the model			
Cut point	Sensitivity	Specificity	Positive predictive value	Negative predictive value
≥1 (one or more factor present)	88.89	34.55	18.18	95
≥2 (two or more factors present)	66.67	89.09	50	94.23
>3 (three or more factors present)	22.22	100	100	88.71

CI, confidence interval; CMV, cytomegalovirus; IRS, immune reconstitution syndrome; OR, odds ratio.

IRS occurred in 4.2% (1/24) of the subjects with none of the factors, 8.3% (2/24) with one factor, 30.8% (4/13) with two factors, and 66.7% (2/3) with all three factors (χ^2 for trend P=0.0016). Sensitivity, specificity, and predictive values for the effect of these variables on the risk of IRS are shown in Table 4.

Outcomes

The overall mortality in the patients was 17.2% (11/64); mortality rate was 33.3% (3/9) in 9 patients with IRS and 14.5% (8/55) in 55 patients without IRS (P=0.311). None of the deaths were attributable to IRS. Causes of death in three patients with IRS were hepatitis C virus recurrence, candidemia, and septic shock in one patient each, respectively.

DISCUSSION

Several observations from our study have relevant implications regarding TB in SOT recipients. IRS was documented in 14% of the transplant recipients with TB. This rate is similar to the frequency of TB-associated IRS in other HIV-negative hosts. IRS developed in 10% to 15.4% of the HIV-negative patients, a median of 56 to 87 days after initiation of anti-TB therapy (*14, 18*). HIV-negative patients with IRS were more likely to have extrapulmonary disease at initial diagnosis, lower baseline lymphocyte count, and a greater increase in lymphocyte count during IRS (*14*). In HIV-positive patients, the rates of TB-associated IRS are higher and range from 8% to 43% (*15*). Lower CD4 counts, disseminated and extrapulmonary TB, a shorter delay between anti-TB and ART initiation, and a robust immunologic and virological response to ART were risk factors for IRS (*15*).

To our knowledge, only two case reports of TB-associated IRS in SOT recipients have been reported previously (*12, 13*). A 29-year-old renal transplant recipient developed tuberculous pleurisy 19 months after transplantation. One month after initiation of anti-TB therapy, persistent high fever with worsening radiographic findings developed. Repeat diagnostic workup was nonrevealing, and the symptoms and pulmonary lesions improved spontaneously without change in medications or immunosuppressants. The second case was a 28-year-old heart-lung transplant recipient with culture-confirmed pulmonary TB 81 days after transplantation (*12*). While receiving four-drug anti-TB therapy, hectic fever and worsening pulmonary

TABLE 4. Multivariate analysis of factors associated with immune reconstitution syndrome (Model 2)

Factor	Reference Group	OR (95% CI)	*P*
Liver transplantation	No liver transplantation	4.682 (0.89–24.39)	0.067
Extrapulmonary TB	No extrapulmonary TB	2.203 (0.41–11.63)	0.352
CMV infection	No CMV infection	4.342 (0.82–23.11]	0.085
Risk of IRS			
One of the above factors	None of the above	2.091 (0.17–24.73)	0.558
More than one of the above factors	None of the above	13.8 (1.46–130.07)	0.022
Diagnostic accuracy and estimates of probability of IRS using liver transplantation, extrapulmonary TB, and CMV infection in the model			
Cut point	Sensitivity	Specificity	Positive predictive value	Negative predictive value
≥1 (one or more factor present)	88.89	41.82	20	95.8
≥2 (two or more factors present)	66.67	81.82	37.5	93.75
≥3 (all three factors present)	22.22	98.18	66.67	88.52

CMV, cytomegalovirus; IRS, immune reconstitution syndrome; TB, tuberculosis.

infiltrates developed on day 131, which ultimately resolved with corticosteroids. A bronchoalveolar lavage yielded markedly activated alveolar $CD4^+$ T lymphocytes that produced interferon γ in response to tuberculin, suggesting that the lymphocytic response was probably related to TB (*19*).

Our study is the first to systematically assess the characteristics, risk factors, and outcomes of TB-associated IRS in SOT recipients using standardized criteria. IRS developed a median of 47 days after the initiation of anti-TB therapy. Worsening or new-onset pulmonary infiltrates, pleural/pericardial effusion, unexplained fever, lymphadenopathy, and CNS tuberculoma with hydrocephalus were the most common presenting features. With the exception of once case (patient 2; Table 1). IRS occurred within 100 days of initiation of anti-TB therapy in all but one patient. Patient 2 developed tuberculoma and hydrocephalus, which are known manifestations of IRS 103 days after completion of 12 months of anti-TB therapy. Delayed occurrences of TB-related IRS have been reported in other hosts (*20*). Three of nine patients with IRS died within the follow-up period; however, the deaths were not deemed attributable to IRS (Table 1).

Liver transplantation was an independently significant risk factor for IRS in our study (adjusted OR, 6.1; P=0.041). Previous studies have shown that liver transplant recipients have a propensity to have more fulminant disease expression, greater severity of infections, and a higher rate of disseminated disease caused by opportunistic infection (*21–23*). Indeed, liver transplant compared with other SOT recipients in our study were more likely to have extrapulmonary and CNS TB. Disseminated and extrapulmonary disease conferred a higher risk of IRS in diverse hosts with TB and in SOT recipients with other opportunistic infections (*14, 24*). Thus, although our observations regarding a higher risk of TB-associated IRS in liver transplant recipients may be reflective of a greater likelihood of extrapulmonary disease in these patients, it is possible that other unmeasured or unknown variables that posed a risk for IRS in liver transplant recipients were not assessed in our study.

It is well recognized that CMV is an immunosuppressive virus and that a higher degree of immunosuppression at the onset of disease is predictive of subsequent IRS (*25*). Prior CMV infection conferred a 5.65-fold higher risk of IRS in our study (Table 3). It is plausible that CMV led to an overall greater net state of immunosuppression. Conversely, CMV infection may have been the result of a more immunocompromised state at baseline in patients with IRS.

Although not independently significant, rifampin use was associated with a 4.5-fold higher risk of IRS in our analysis (Table 3). Rifampin possesses potent bactericidal activity against organisms that are dividing rapidly (early bactericidal activity) (*26*) or semidormant (*27*). As a result, on rifampin initiation, the bacterial load of M. tuberculosis might decrease rapidly. On the other hand, rifampin also has the potential for causing a marked reduction in the levels of CNI. Taken together, the initial balance between M. tuberculosis and host immunity may be changed toward proinflammatory status more significantly after rifampin use than other anti-TB agents, and this might predispose to the development of IRS.

We showed that the presence of more than one risk factor (liver transplantation, CMV infection, and rifampin use), when compared with none of these factors conferred, a 19-fold increase in the risk of IRS (model 1; Table 3). Likewise, the presence of more than one factor (liver transplantation, CMV infection, and TB with CNS disease), when compared with none of these, seemed to add an approximately 13-fold increase in the risk of IRS (model 2; Table 4).

Reduction in immunosuppression has been shown to be a risk factor for IRS in SOT recipients with other opportunistic infections (*8, 24*). Discontinuation of CNI was an independently significant risk factor for Cryptococcus-associated IRS in SOT recipients (*28*). However, we were unable to show an association between TB-related IRS and reduction

TABLE 5. Criteria for immune reconstitution syndrome

Diagnosis of IRS
A. New or worsening of any of the following after diagnosis of tuberculosis:
(a) Lymphadenopathy, cold abscess, or other focal tissue involvement, for example, tuberculous arthritis
(b) Radiologic features of tuberculosis (found by chest radiography, abdominal ultrasonography, CT, or MRI)
(c) CNS tuberculosis (meningitis or focal neurologic deficit, for example, that caused by tuberculoma)
(d) Serositis (pleural effusion, ascites, or pericardial effusion)
(e) Constitutional symptoms such as fever, night sweats, or weight loss
(f) Abdominal pain accompanied by peritonitis, hepatomegaly, splenomegaly, or abdominal adenopathy
B. Symptoms occurred during receipt of appropriate antituberculous therapy and could not be explained by the following explanations:
(a) Failure of tuberculosis treatment because of tuberculosis resistance
(b) Poor adherence to tuberculosis treatment
(c) Another opportunistic infection or neoplasm (it is particularly important to exclude an alternative diagnosis in patients with smear-negative pulmonary tuberculosis and extrapulmonary tuberculosis where the initial tuberculosis diagnosis was not microbiologically confirmed)
C. Negative results of cultures for Mycobacterium tuberculosis during the diagnostic workup for the inflammatory process[a]

Definitions are based on references and are modified for use in a transplantation setting (*15, 31*).

[a] Patients in whom the sites of original infection that yielded Mycobacterium tuberculosis were inaccessible for follow-up cultures would be considered as having negative cultures.

CNS, central nervous system; CT, computed tomography; IRS, immune reconstitution syndrome; MRI, magnetic resonance imaging.

in immunosuppression or the specific immunosuppressant agents reduced in our study (Table 2). It is known that M. tuberculosis per se causes profound suppression of host immune responses against these bacteria, and its control with anti-TB therapy in itself can result in IRS. IRS is a well-recognized entity in immunocompetent hosts with TB in whom the use of anti-TB therapy alone is adequate to reverse pathogen-induced immunosuppression and promote sufficient enhancement of immunity to cause IRS. Thus, it is plausible that the reversal of pathogen-induced immune suppression with anti-TB therapy along with the use of rifampin-based regimens were enough to result in IRS, regardless of significant reduction in immunosuppressive regimen in our patients. In addition, the number patients in whom immunosuppression was discontinued or reduced on diagnosis in our study was small; CNI was discontinued in only three patients (4.6%), and prednisone, in 2 patients (3%) (Table 2). These data suggest that care providers generally did not make significant changes in immunosuppressive regimen in patients with TB. This may also have accounted for the low rates of rejection observed in patients with IRS in this study (11%) as opposed to those observed in Cryptococcus-associated IRS in SOT recipients (66%) (*29*, *30*). Change in immunosuppression at the time of CMV infection in patients with and without IRS is shown in Table 2.

Several weaknesses of our study deserve to be acknowledged. It is possible that some patients diagnosed by nonculture base criteria did not have TB; however, this is unlikely because all patients were treated with therapy specifically against M. tuberculosis with resolution of their symptoms/signs. Although previously proposed and standard definitions were used for the diagnosis of IRS (*15*, *31*), reliable biologic markers or laboratory assays that can unequivocally diagnose IRS do not exist, and there are no criteria of IRS specifically for SOT recipients. Thus, it is possible that some cases may have been misdiagnosed. Because the study was based on data generated as routine clinical care, assessment of the net state of immunosuppression or immunologic assays for the determination of the impairment or recovery of immune responses was not performed. Strengths of our study include the systematic collection of data using uniform data collection tool and that this was a multicenter study that renders our findings generalizable.

Recognition of IRS as an entity distinct from progressive or worsening disease has implications relevant for the optimal management of TB in transplant recipients and for avoiding unnecessary and unwarranted changes in antituberculous therapy. TB-associated IRS seems to develop in 14% of the SOT recipients with TB. We have identified readily assessable and clinically identifiable factors that may be useful in predicting the risk of TB-associated posttransplantation IRS. Future studies are warranted to discern the precise immunologic basis of posttransplantation TB-associated IRS.

MATERIALS AND METHODS

The study population composed of SOT recipients diagnosed with TB at the participating centers between 2003 and 2011. Patient management and antituberculous therapy were per standard practice at the transplantation centers. Data generated as standard of care were collected in an observational fashion, and no study-specific interventions or procedures were used. Data collected included demographic characteristics, type of organ transplant, prior transplantation, CMV infection (diagnosed by positive antigenemia or viremia by polymerase chain reaction–based assay) and CMV disease as previously described (*32*), rejection within 6 months before TB diagnosis, renal failure at baseline (defined as serum creatinine >2 mg/dL at the time of diagnosis), immunosuppressive regimen at the time of diagnosis, results of tuberculin skin test, history of prophylaxis for latent TB infection, prior TB diagnosis and treatment, symptoms and signs at TB presentation, approximate date of the onset of TB, anti-TB therapy use and treatment duration, management of immunosuppressive therapy after the initiation of anti-TB therapy, and outcomes at 12 months after the initiation of anti-TB therapy. IRB approval was per local requirements.

The diagnosis of TB was made according to the World Health Organization established criteria of smear-positive pulmonary TB, smear-negative pulmonary TB, or extrapulmonary TB (*33*). TB of an organ other than the lungs, for example, pleura, lymph nodes, abdomen, genitourinary tract, skin, joints and bones, and meninges, was considered as extrapulmonary TB (*33*). IRS was defined as based on the case definitions proposed by Singh and Perfect (*31*) and the International Network for the Study of HIV-associated IRS (modified for use in a transplantation setting) (*15*) (Table 5).

Statistical Analyses

Statistical analyses were performed using Intercooled Stata version 12.0 (Stata Corp, LP; College Station, TX). Categorical data were compared using the chi-square test or Fisher exact test. Continuous variables were compared using the rank-sum test. A logistic model was constructed to estimate the effect of multiple factors on the primary outcome for IRS. Sensitivity, specificity, and predictive values were calculated for estimating the value of using the occurrence of multiple risk factors to predict the likely outcome classification.

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