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Clinical Outcomes of Tuberculosis in Renal Transplant Recipients

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Tuberculosis (TB) is an important cause of morbidity and mortality in renal transplant recipients. Rifampin has a potent sterilizing activity, but it reduces the serum concentrations of the immunosuppressive agents. Moreover, the possible contribution made by mycobacterial infection to the incidence of graft rejection or renal dysfunction remains unclear. In this study, we investigated the recurrence of TB and graft survival duration according to rifampin usage, and we evaluated the factors that could influence the duration time until the recurrence of TB. Seventy-eight TB patients diagnosed after kidney transplantation were studied. Pulmonary TB was diagnosed in 26 of the 78 patients (33.3%), pleural TB in 23 (29.5%), combined pulmonary and pleural TB in 5 (6.4%), miliary TB in 19 (24.4%), and intestinal TB in 2 patients. In the pulmonary (pulmonary TB and pleural TB) TB group, no differences in graft survival and the TB free duration period were observed between the rifampin usage subgroup and the non-rifampin usage subgroup. In the extrapulmonary TB group, no difference was found in mean graft survival time between the rifampin usage subgroup and the non-rifampin usage subgroup, but the rifampin usage subgroup showed that the TB had a tendency to recur later than for the non-rifampin usage subgroup (87 ± 8 vs. 44 ± 7 months, respectively, p=0.30). The factor affecting the duration period until the recurrence of TB was the treatment duration (RR=0.761, p=0.030). This study suggests that rifampin does not affect graft survival in renal transplant recipients in whom immunosuppression is carefully monitored. Also, the study results indicate that rifampin may prevent a recurrence of extrapulmonary tuberculosis. Prolonged treatment appears to be appropriate for renal transplant recipients with TB.

Key Words: Tuberculosis, renal transplantation, rifampin, drug interaction, treatment duration

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INTRODUCTION

Tuberculosis (TB) is the leading cause of death worldwide due to a single infectious disease, and it kills more than 2 million people each year.[1] This global epidemic is insidious and growing and especially in developing countries, where the disease is endemic.

The incidence of TB in immunosuppressed patients is expected to rise. Renal transplant recipients are considered to be at special risk of reactivating old tuberculous lesions due to their clinically-induced chronic immunosuppression. In the case of renal transplant recipients with TB, the drugs used to treat TB affect the metabolism of many of the immunosuppressive drugs, and this can result in a lack of efficacy and/or toxicity.[2] The majority of such clinically relevant drug-to-drug interactions involving the antituberculosis drugs involve the rifamycins (rifampin, rifabutin and rifapentine). The rifamycins act on a variety of metabolic pathways, and particularly on those involving isozymes of the cytochrome P450 system. Hence, by inducing the activities of metabolic enzymes, rifamycin therapy reduces the serum concentrations of many drugs, sometimes to sub-therapeutic levels. The rifamycins differ substantially in terms of their potencies as enzyme inducers; rifampin is the most potent, rifapentine is intermediate and rifabutin the least potent.[3]

Some of these drug-to-drug interactions can be managed with close clinical or laboratory monitoring, and by increasing the doses of medications affected by the rifamycins. In other cases, the magnitude of reduced serum concentrations cannot be restored by dose increases. In the case of renal transplantation, rifamycins reduce the concentrations of immunosuppressive agents such as cyclosporine[4,5] and corticosteroid.[6] Thus, drug-to-drug interactions between antituberculous drugs and immunosuppressive agents are central to the management of TB in transplantation patients. In some situations, rifabutin can sometimes be used in place of rifampin, when an unacceptable drug-drug interaction is noticed between rifampin and another drug, like with cyclosporine.[4] However, because rifabutin is not available in South Korea, rifampin is generally not included in TB treatment regimens of kidney transplant patients because of the fear of kidney rejection.

In South Korea the incidence of TB in the general population is much higher than in the West. In 2001, 79 new cases of TB per 100,000 people were reported in South Korea, compared to 6 new cases per 100,000 in the USA.[7] Moreover, in Korea, the incidence of TB in renal transplant recipients is much higher (776 new cases per 100,000 per year[8]) than in the general population, and the primary resistance rate of TB is for too high (5.8% in 1995[9]).

In this study, we investigated the treatment success rate, recurrence duration and graft survival duration for renal transplant recipients with TB according to the TB treatment regimens; we also examined the factors affecting the TB recurrence duration in a geographic area of Korea with endemic TB.

MATERIALS AND METHODS

The clinical records of kidney transplant recipients were reviewed for all the transplants performed at Yonsei University College of Medicine, Severance Hospital from January 1979 to December 2002. The data collected for analysis included: TB occurrence; graft origin; immunosuppressive regimens; TB sites and the mean time of onset after transplantation; immunosuppressive drugs administered during TB treatment; antituberculous drug regimen; graft loss during or after TB treatment; graft survival duration after TB treatment; success or failure and the duration of TB treatment; recurrence of TB after treatment; and the period of time until the recurrence of TB after treatment.

A diagnosis of TB was classified as definite, probable or suspected. A definite case was defined as a positive result for acid-fast bacilli (AFB) on culture testing. A probable case was defined as a positive result on an AFB smear and/or chronic granulomatous inflammation by histopathology and/or other positive laboratory findings consistent with TB (i.e., high levels of adenosine deaminase, a positive TB PCR result in appropriate samples). A suspected case was defined as having the typical TB findings by radiology or if the patient had the clinical features of TB, and there was improvement for the patient after TB treatment.[10,11]

Drug-to-drug interactions were managed with close clinical and/or laboratory monitoring of dosage increases of the medications affected by the antituberculous medications. We increased the cyclosporine doses with frequent monitoring of the patients' serum concentrations. Corticosteroid doses were increased two fold with close clinical monitoring of patients.

Patients having a treatment duration of less than 6 months due to the side effects of antituberculous drugs or who died during treatment due to unrelated causes were excluded from analysis.

The statistical analysis was performed with Fisher's exact test and the t-test for the comparison of qualitative and quantitative variables, respectively. Graft survival according to rifampin usage was estimated by Kaplan-Meier survival analysis, and we considered death and TB recurrence with a functioning graft as censored data. TB recurrence according to rifampin usage was estimated by Kaplan-Meier survival analysis, and we considered death and graft loss without TB recurrence as censored data. Comparison between survival curves was performed by means of a log-rank test. Cox regression was used to obtain the factors affecting the TB recurrence duration. Significance was accepted for a p-value of < 0.05.

RESULTS

From January 1979 and December 2001, 78 TB patients met the inclusion criteria, and 62 (79.5%) of these patients were male. The mean age of the patients at the time of diagnosis for TB was 39 ± 11 years. Forty-two (53.8%) had received an organ from a living related donor, 34 (43.6%) had received an organ from a living unrelated donor and 2 had received an organ from a cadaveric donor.

The mean time to diagnosis of TB after transplantation was 48 ± 41 months.

Sites of the disease

Pulmonary TB was diagnosed in 26 patients (33.3%), pleural TB in 23 patients (29.5%), combined pulmonary and pleural TB in 5 (6.4%), miliary TB in 19 (24.4%), and intestinal TB in 2 (Fig. 1).

Diagnosis of tuberculosis

According to the diagnostic criteria, 19 patients (24.4%) had definite TB, 42 (53.8%) had probable TB, and 17 patients (21.8%) had suspected TB.

Tuberculosis treatment regimens in renal transplant recipients

Various regimens were used to treat TB in renal transplant recipients. Regimens containing rifampin were used in 35 patients (44.9%) and those without rifampin in 43 (55.1%, Table 1).

Treatment outcomes and graft survival after a diagnosis of tuberculosis in renal transplant recipients according to rifampin usage

To determine the success rates, rejection during treatment and graft survival after a diagnosis of TB according to regimen, we divided the patients

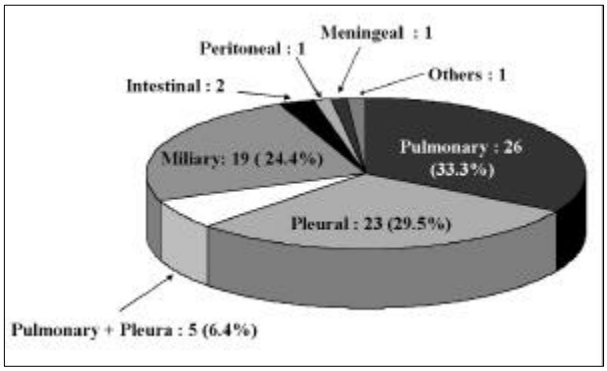

Fig. 1. Sites of tuberculosis after renal transplantation.

Table 1. Tuberculosis Treatment Regimens

Regimen	Number of patients (%)		
	Pulmonary TB group (N=54)	Extrapulmonary TB group (N=24)	Total (N=78)
With rifampin	21 (38.9)	14 (58.3)	35 (44.9)
HERZ	3 (5.6)	3 (12.5)	6 (7.7)
HER	6 (11.1)	3 (12.5)	9 (11.5)
SHER	3 (5.6)	3 (12.5)	6 (7.7)
HRZ	9 (16.6)	2 (8.3)	11 (14.2)
SHRZ	0	3 (12.5)	3 (3.8)
Without rifampin	33 (61.1)	10 (41.7)	43 (55.1)
HEZ	15 (27.8)	5 (20.8)	20 (25.6)
SHEZ	18 (33.3)	5 (20.8)	23 (29.5)

H, Isoniazid; E, Ethambutol; R, Rifampin; Z, Pyrazinamide; S, Streptomycin.

into 2 groups, a 'pulmonary' infection group and an 'extrapulmonary' infection group. The pulmonary group (n=54) included pulmonary and pleural TB patients, and the extrapulmonary group (n=24) included TB patients with other than pulmonary TB and pleural TB. In addition, each of these groups was further divided into 'Rifampin subgroups' and 'Non-rifampin subgroups', depending on rifampin use.

In the pulmonary group, the graft survival period after a diagnosis of TB was 101 ± 15 months for those that received rifampin (n=21) and 84 ± 6 months for those that did not receive rifampin (n=33), with no statistical significance being noted between the groups (Fig. 2). The success and rejection rates during TB treatment also showed no difference between the rifampin subgroups (Table 2).

In the extrapulmonary group, the mean graft survival period after the diagnosis of TB was 67 ± 13 months in the rifampin subgroup (n=14), and 70 ± 2 months in non-rifampin subgroup (n=10), with no statistical significance being noted (data not shown). The success and rejection rates during TB treatment were not different for these

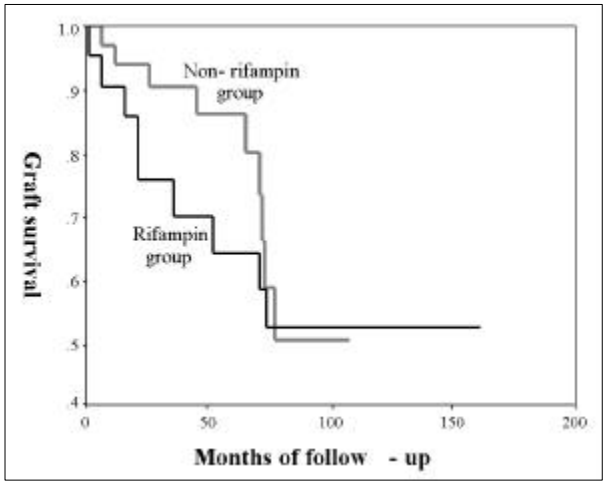

Fig. 2. Graft survival in renal transplant recipients according to rifampin usage in the pulmonary TB group.

Table 2. Clinical Feature and Therapeutic Results for the 'Pulmonary' TB Group in Renal Transplant Recipients

	Rifampin subgroup (N=21)	Non-rifampin subgroup (N=33)
Sex (M:F)	19 : 2	26 : 7
Age at diagnosis of TB (years)	38 ± 11	37 ± 12
Mean time from transplant to TB (months)	38 ± 26	59 ± 49*
Hypertension	7 (33%)	22 (67%)*
Donor		
Living related donor	9 (43%)	23 (70%)
Living unrelated donor	11 (52%)	9 (27%)
Cadaver	1 (5%)	1 (3%)
Immunosuppression		
Corticosteroid	21 (100%)	32 (97%)
Cyclosporine	18 (86%)	31 (94%)
Azathioprine	7 (33%)	10 (30%)
Mycophenolate mofetil	0	2 (6%)
Duration of therapy (months)	10.3 ± 4.5	12.9 ± 3.3*
Rejection during therapy	2 (10%)	2 (6%)
Failure to treatment	3/19 (16%)	1/31 (3%)†

*$p<0.05$ by t-test or Fisher's exact test.
†Rejection cases during therapy were excluded from analysis.

two subgroups (Table 3).

Duration until the recurrence of TB after successful treatment according to rifampin usage

In the pulmonary group, the recurrence duration period was 127 ± 12 months in the rifampin subgroup and 85 ± 5 months in the non-rifampin subgroup, without there being any statistical significance (Fig. 3).

In the extrapulmonary group, the recurrence duration period was 87 ± 8 months in the rifampin subgroup and 44 ± 7 months in the non-rifampin subgroup, indicating there was a tendency toward later recurrence in the rifampin group, but this was without statistical significance (p=0.30, Fig. 4).

Factors affecting the recurrence of TB after successful treatment

Sixty-three patients were treated successfully without organ rejection. Multivariate Cox analysis showed that the factor associated with the duration until the recurrence of TB was the TB treatment duration. The relative risk (RR) conferred by this factor was 0.761 (Table 4). In regard of TB recurrence, the outcomes of the patients who had been treated for more than 12 months were more

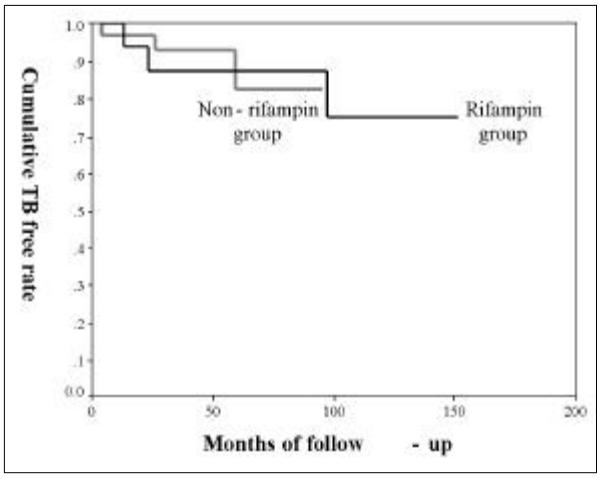

Fig. 3. TB free duration after successful treatment in the pulmonary TB group.

Table 3. Clinical Features and Therapeutic Results of the 'Extrapulmonary' TB Group in Renal Transplant Recipients

	Rifampin subgroup (N=14)	Non-rifampin subgroup (N=10)
Sex (M:F)	9 : 5	8 : 2
Age at diagnosis of TB (years)	42 ± 12	42 ± 12
Mean time from transplant to TB (months)	36 ± 39	49 ± 37
Diabetes mellitus	2 (14%)	6 (60%)*
Donor		
Living related donor	5 (36%)	5 (50%)
Living unrelated donor	9 (64%)	5 (50%)
Immunosuppression		
Corticosteroid	13 (93%)	10 (100%)
Cyclosporine	13 (93%)	9 (90%)
Azathioprine	6 (43%)	2 (20%)
Mycophenolate mofetil	0	2 (20%)
Duration of therapy (months)	10.1 ± 7.1	12.1 ± 5.2
Rejection during therapy	3 (21%)	0
Failure to treatment	2/11 (18%)	3/10 (30%)†

*p<0.05 by Fisher's exact test.
†Rejection cases during therapy were excluded from analysis.

Table 4. Multivariate Analysis of Factors Affecting the Recurrence Duration after Successful TB Treatment, Cox Proportional Hazards Regression

Factor	Relative risk (RR)	95% Confidence interval (CI)	*p*
Monthly increases in treatment duration	0.761	0.595 - 0.973	0.030
Sites of TB (pulmonary group v extrapulmonary group)	0.333	0.073 - 1.533	0.158
Number of TB treatment drugs (3 v 4)	2.010	0.366 - 11.038	0.422
Rifampin usage (with rifampin vs without rifampin)	0.501	0.106 - 2.358	0.382

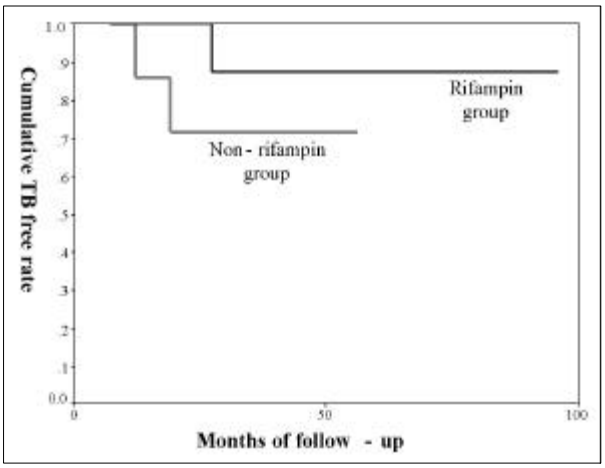

Fig. 4. TB free duration after successful treatment in the extrapulmonary TB group.

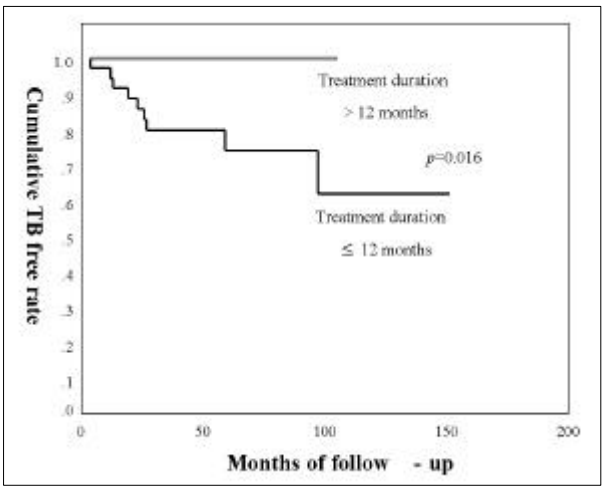

Fig. 5. TB free duration in patients whose treatment duration had been more than 12 months compared with patients whose treatment duration had been 12 months or less. Significance was calculated by means of log-rank test.

favorable than those of the patients who had been treated for 12 months or less (p=0.016, Fig. 5).

DISCUSSION

TB has a major impact on renal transplantation in endemic regions because cellular immune impairment can facilitate the reactivation of dormant bacilli residing in residual lesions or the development of an uncontained primary infection. In the transplant setting, TB may be contracted by the inhalation of airborne bacilli, or more commonly, TB may emerge due to the reactivation of dormant lesions. It is significant that the incidence of TB in transplant recipients has been consistently reported as several-fold higher than in the general population. Moreover, the risk of developing TB after transplantation is directly related to the local epidemiological risk. The incidence of TB in transplant recipients in the United States has been reported to be between 0% and 1.3%.[12] A research series from Spain showed that 0.8[13] - 1.6%[14] of transplant recipients developed TB. In contrast, for countries with high rates of TB in the general population, its incidence in transplant patients is much higher, i.e., 3.5% in Saudi Arabia,[15] 11% in South Africa,[16] 11.8% in India,[17] and 14.5% in Pakistan.[18]

The possible contribution made from mycobacterial infection to the incidence of graft rejection or renal dysfunction remains unclear. However, regardless of the source of infection, the treatment of TB in kidney transplant patients requires that the utmost attention be paid to the specifics of the antimicrobial therapy, and to the management of the immunosuppressive agent/drug interactions. The appropriate level of immunosuppression must be determined for each individual patient. Rifampin is a first-line choice of drug for TB treatment, and the potent sterilizing and mycobactericidal activity of rifampin has

changed TB therapy by allowing treatment to be shortened from 18 months to 6-9 months. However, the interaction between the rifamycins (rifampin, rifabutin, rifapentine) and the immunosuppressive drugs requires special care. All of the rifamycins are inducers of the various isozymes of the cytochrome P450 system and thus, they reduce the cyclosporine serum levels.[4,5] Of all the rifamycins, rifampin is the most potent enzyme inducer.[3] Hence, the cyclosporine doses must generally be increased, and its serum levels monitored very closely. A two to three fold increase in the normal corticosteroid dose has been recommended in such situations because of the effect that rifampin has on corticosteroid catabolism.[6,13] It should be noted that the use of rifampin for TB patients with a renal transplant is somewhat controversial. Aguado et al. have suggested that the use of rifampin should be avoided in patients receiving cyclosporine, as drug-to-drug interference between the two could lead to organ rejection.[13] In the present study, however, there were no differences in graft survival observed according to rifampin use. Therefore, we can state that with careful monitoring of patients' immunosuppression, rifampin does not, given the limitations of the present study, affect graft survival.

Rifampin has a potent sterilizing activity, and it is active against the intracellular, slowly replicating TB bacilli, and it is also somewhat active against the nearly dormant TB organisms residing in necrotic foci.[19] Moreover, rifampin was found to reduce the recurrence rate of TB.[20] In the present study, we observed a tendency for TB to recur later in the extrapulmonary TB group patients (87 ± 8 vs 44 ± 7 months, p=0.30) who were administered with rifampin, although this relation did not carry significance, which we attribute to the small number of cases. In the pulmonary TB group, there was no observed difference for the TB free duration period after treatment with respect to rifampin use.

Some study limitations should be mentioned. First, rifampin was usually used only in more severe TB cases, but TB severity was not included as a study variable because of the study's retrospective nature. Second, in the pulmonary TB group, the duration period from transplantation to the diagnosis of TB and the duration period of therapy were longer in the non-rifampin subgroup than in the rifampin subgroup (Table 2). This bias probably had an influence on the duration period until the recurrence of TB after treatment. Therefore, in the pulmonary TB group, the role of rifampin on time of TB recurrence remains an issue. Finally, it is not clear whether TB recurrence was due to reactivation of dormant lesions or if it was due to reinfection.

In the case of HIV infected patients, 6 months should be considered the minimum duration of treatment for TB in adults. If there is any evidence of a slow or suboptimal response (e.g., the cultures are still positive after 2 months of therapy), prolongation of the continuation phase to 7 months (a total of 9 months treatment) should be strongly considered.[2] Although there is no clinical consensus regarding the optimal treatment for renal transplant recipients with TB, a recent series supports prolongation of therapy, and the study showed a lower mortality for patients receiving more than 9 months of treatment.[13] In the present study, the factor associated with the recurrence of TB was treatment duration (relative risk=0.761, p=0.030). None of the patients treated for more than 12 months (n=25, mean follow-up duration: 54 months) suffered from a recurrence of TB. Moreover, the outcomes of the patients who had been treated for more than 12 months were more favorable than those outcomes of the patients who had been treated for 12 months or less (Fig. 5). Therefore, a prolonged treatment of probably more than 12 months appears to be appropriate in renal transplant recipients with TB, in a TB endemic area.

In conclusion, the findings of this study suggest that rifampin does not affect graft survival in renal transplant recipients when the physician institutes careful immunosuppression monitoring. In addition, the study suggests that rifampin may prevent the recurrence of extrapulmonary tuberculosis, and prolonged treatment appears to be appropriate clinical strategy for renal transplant recipients with TB.

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