

Clinical Outcomes of Tuberculosis in Renal Transplant Recipients according to the Use of Rifampin

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Thesis By

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Abstract

Clinical Outcomes of Tuberculosis in Renal Transplant Recipients according to the Use of Rifampin

Background: Tuberculosis (TB) is an important cause of morbidity and mortality in renal transplant recipients. And rifampin has potent sterilizing activity but reduces the serum concentrations of immunosuppressive agents by inducing various isozymes of the cytochrome P450 system. Moreover, the possible contribution made by mycobacterial infection to the incidence of graft rejection or renal dysfunction remains unclear. The treatment of TB in kidney transplant patients requires attention in terms of the antimicrobial therapy adopted and in terms of the management of the immunosuppressive agents used and potential drug interactions.

Materials and methods: Seventy-eight TB patients diagnosed after kidney transplantation at Yonsei University College of Medicine, Severance Hospital, between January 1979 and December 2002 were enrolled in this study. Data collected for analysis included: graft origin; immunosuppressive regimen; TB site; mean time to TB onset after transplantation; immunosuppressive drugs administered during TB treatment; antituberculous drug regimen; graft survival duration after TB treatment; success or failure, and duration of the TB treatment; recurrence of TB after treatment; and duration of TB recurrence after treatment.

Results: 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 mean graft survival and TB free duration 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 between the rifampin usage subgroup and the non-rifampin usage subgroup, but the rifampin usage subgroup showed a tendency to recur later than the non-rifampin usage subgroup (87 ± 8 vs. 44 ± 7 months, $p=0.30$).

Conclusion: This study suggests that rifampin does not affect graft survival in

renal transplant recipients in whom immunosuppression is carefully monitored. Also, indicates that rifampin may prevent recurrence of extrapulmonary tuberculosis. In the case of pulmonary tuberculosis, the role of rifampin on TB recurrence remains an issue.

Key Words: tuberculosis, renal transplantation, rifampin, drug interaction

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I. Introduction

Tuberculosis (TB) is the leading cause of death due to a single infectious disease worldwide, and kills 2 million people each year¹. This global epidemic is growing and becoming more insidious, and 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 chronic immunosuppression, especially in developing countries, in which the disease is endemic.

In the case of renal transplant recipients with TB, drugs used to treat the TB affect the metabolism of many other drugs, and can result in a lack of efficacy and/or toxicity². The majority of such clinically relevant drug-drug interactions involving antituberculosis drugs involve the rifamycins (rifampin, rifabutin, and rifapentine). The rifamycins induce a variety of metabolic pathways, particularly 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 subtherapeutic levels. The rifamycins differ substantially in terms of their potencies as enzyme inducers; rifampin being the most potent, rifapentine intermediate, and rifabutin the least potent³. Some of these drug-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 cases of renal transplantation, rifamycins reduce the concentrations of immunosuppressive agents, such as cyclosporine^{4,5} and corticosteroid⁶. Thus, drug-drug interactions between antituberculous drugs and immunosuppressive agents are central to the management of TB. 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 cyclosporine⁴. However, because rifabutin is not available in South Korea, rifampin is generally not included in TB treatment regimens, 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 of the population were reported in South Korea, compared to 6 new cases per 100,000 in the USA⁷. Moreover in Korea, the incidence of TB in renal transplant recipients is much higher (776 new cases per 100,000 per year⁸) than in the general population, and the primary resistance rate of TB is high (5.8% in 1995⁹).

In this study, we investigated the treatment success rate, recurrence duration, and graft survival duration in renal transplant recipients with TB, according to the TB treatment regimen, in a TB endemic area.

II. Materials and Methods

The clinical records of kidney transplant recipients were reviewed for all transplants performed at Yonsei University College of Medicine, Severance Hospital, between January 1979 and December 2002. The data collected for analysis included: TB occurrence; graft origin; immunosuppressive regimen; TB site 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 duration of TB recurrence 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) in culture. A probable case as a positive result for AFB smear and/or chronic granulomatous inflammation by histopathology and/or a laboratory finding consistent with TB (i.e., high levels of adenosine deaminase, a positive TB PCR result in appropriate samples). A suspected case was defined as one having a typical finding by radiology or the clinical features of TB, and improved result after TB treatment.

Patients with 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.

The statistical analysis performed included Fisher's exact test, the t-test and Kaplan-Meier survival analysis for mean time of graft survival and mean time until TB recurrence. Significance was accepted for a p-value of <0.05.

III. Results

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

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

1. 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 (Figure 1).

2. Diagnosis of tuberculosis

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

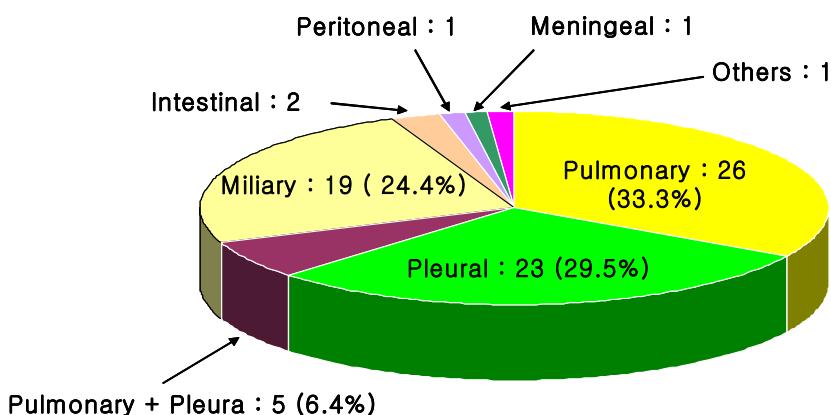


Figure 1. Sites of tuberculosis in renal transplant recipients.

3. 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 in 43 (55.1 %, Table 1).

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.

4. Treatment outcomes and graft survival after a diagnosis of tuberculosis in renal transplant recipients

To determine success rates, rejection during treatment and graft survival after a diagnosis of TB according to regimen, we divided the patients into 2 groups, a 'pulmonary' and an 'extrapulmonary' 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',

dependent on rifampin use.

In the pulmonary group, mean graft survival after a diagnosis of TB was 101 ± 15 months those that received rifampin ($n=21$) and 84 ± 6 months those that did not ($n=33$), with no statistical significance. Success and rejection rates during treatment showed no difference between the rifampin subgroups (Table 2).

Table 2. Clinical features 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	$59\pm 49^†$
Diabetes mellitus	4(19%)	13(39%)
Hypertension	7(33%)	22(67%) [†]
Duration of therapy (months)	10.3 ± 4.5	$12.9\pm 3.3^†$
Rejection during therapy	2(10%)	2(6%)
Mean graft survival after diagnosis of TB (months)	101 ± 15	84 ± 6
Failure to treatment	3/19(16%)	1/31(3%) [‡]

[†] $p<0.05$.

[‡] Rejection cases during therapy were excluded from analysis.

In the extrapulmonary group, mean graft survival 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. The success and rejection rates during treatment were not different for these two subgroups (Table 3).

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%)†
Hypertension	7(50%)	6(60%)
Duration of therapy (months)	10.1±7.1	12.1±5.2
Rejection during therapy	3(21%)	0
Mean graft survival after diagnosis of TB (months)	67±13	70±2
Failure to treatment	2/11(18%)	3/10(30%)‡

† $p<0.05$.

‡ Rejection cases during therapy were excluded from analysis.

5. Recurrence duration after successful TB treatment

In pulmonary group, the mean recurrence duration was 127±12 months in the rifampin subgroup and 85±5 months in the non-rifampin subgroup, without statistical significance (Figure 2).

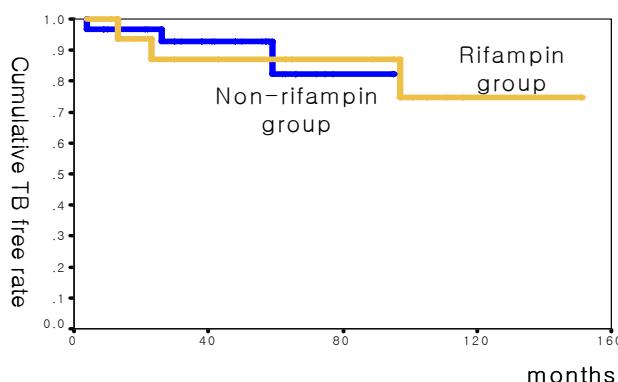


Figure 2. TB free duration after successful treatment in the pulmonary TB group.

In extrapulmonary group, mean recurrence duration was 87 ± 8 months in the rifampin subgroup and 44 ± 7 months in the non-rifampin subgroup, indicating a tendency toward later recurrence in the rifampin subgroup, but without statistical significance ($p=0.30$, Figure 3).

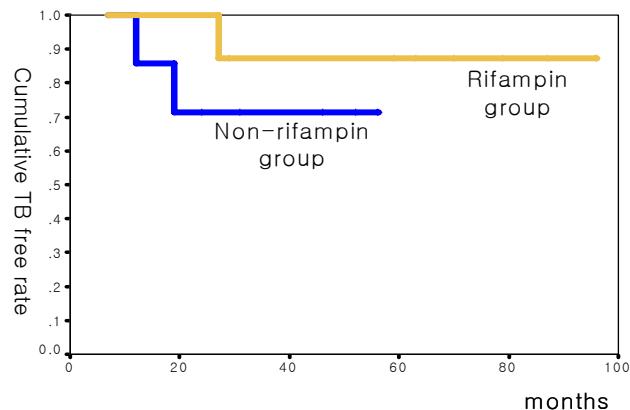


Figure 3. TB free duration after successful treatment in the extrapulmonary TB group.

IV. Discussion

TB has a major impact on renal transplantation in endemic regions, as cellular immune impairment can facilitate the reactivation of dormant bacilli 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. Significantly, the incidence of TB in transplant recipients has been consistently reported to be 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%¹⁰. A series from Spain showed that 0.8¹¹-1.6%¹² of transplant recipients developed TB. In contrast, in countries with high rates of TB in the general population, its incidence in transplant patients is much higher, i.e., 3.5% in Saudi Arabia¹³, 5.5% in South Korea⁸, 11% in South Africa¹⁴, 11.8% in India¹⁵, and 14.5% in Pakistan¹⁶.

The possible contribution made by 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 utmost attention be paid to the specifics of the antimicrobial therapy, and to the management of immunosuppressive agent/drug interactions. The appropriate level of immunosuppression must be determined for each patient. Rifampin is a first-choice drug for TB treatment, the potent sterilizing and mycobactericidal activity of rifampin has changed TB therapy, allowing treatment to be shortened from 18 months to 6-9 months. However, the interaction between the rifamycins (rifampin, rifabutin, rifapentine) and immunosuppressive drugs requires special care. All of the rifamycins are inducers of the various isozymes of the cytochrome P450 system and thus reduce cyclosporine serum levels^{4,5}. Of the rifamycins, rifampin is the most potent enzyme inducer³. Hence, cyclosporine doses must generally be increased, and its serum levels monitored 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^{6,11}. It should be noted that the use of

rifampin in TB patients with a renal transplant is controversial. Aguado et al. suggested that rifampin use should be avoided in patients receiving cyclosporine, as interference between the two could lead to rejection¹¹. In the present study, however, no difference in graft survival was observed according to rifampin use. This means that with careful monitoring of immunosuppression rifampin does not, given the limitations of the present study, affect graft survival.

Rifampin has a potent sterilizing activity and is active against intracellular, slowly replicating bacilli, and also is somewhat active against near dormant organism in necrotic foci¹⁷. Moreover, rifampin was found to reduce the recurrence rate¹⁸. In the present study, and although the relation did not carry significance, which we attribute to the small number of cases, we observed a tendency for TB to recur later in those in the extrapulmonary TB group (87 ± 8 vs 44 ± 7 months, $p=0.30$) administered rifampin. In the pulmonary TB group, no difference in TB free duration after treatment was observed with respect to rifampin use.

Some study limitations should be mentioned. First, rifampin was usually used in more severe TB cases, but TB severity was not included because of the study's retrospective nature. Second, in the pulmonary TB group, the duration from transplantation to the diagnosis of TB and the duration of therapy, were longer in the non-rifampin subgroup than in the rifampin subgroup (Table 2). This bias have probably influenced TB free duration after treatment. Therefore, in the pulmonary TB group, the role of rifampin on TB recurrence remains an issue.

V. Conclusion

The findings of this study suggest that rifampin does not affect graft survival in renal transplant recipients given careful immunosuppression monitoring. In addition, the study suggests that rifampin may prevent the recurrence of extrapulmonary tuberculosis. However, in the case of pulmonary tuberculosis, further study is needed.

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국문요약

신장 이식 환자에서 항결핵 치료시 리팜핀 사용 여부에 따른 결과 분석

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신이식 환자는 면역저하제 치료로 인하여 면역력이 저하되어 있어 결핵의 발병률이 높다. 특히 결핵의 유병률이 높은 지역에서는 더욱 그러하다. 리팜핀은 결핵의 치료에 사용되는 1차 약제로 강력한 멸균작용이 나타내지만, cytochrome P450의 여러 동종효소를 유도하여 리팜핀과 같이 사용되는 다른 약제의 혈중농도를 심각하게 저하시키는 약물 상호작용을 나타낸다. 신이식환자가 결핵에 이환되어 리팜핀이 포함된 병용요법으로 치료를 받을 경우, 면역억제제로 사용되는 cyclosporine과 corticosteroid의 혈중 농도를 저하시켜 이식신 거부반응의 위험성이 증가한다. 신장이식환자에서 결핵 및 결핵의 치료가 이식신 생존기간에 어떠한 영향을 미치는지 명확히 알려져 있지 않다. 따라서 본 연구에서는 신이식 환자가 결핵에 이환되었을 경우, 리팜핀의 사용 여부에 따라 이식신 생존기간과 치료 후에 결핵 재발율의 차이를 알아보고자 하였다.

연세대학교 의과대학 세브란스병원에서 1979년부터 2002년까지 신장 이식 후에 결핵에 이환된 환자의 침범 장기, 이식 후 결핵에 이환된 기간, 면역억제 용법, 항결핵 병용요법, 치료중 이식신 거부반응 여부, 치료 후 거부반응 여부 및 거부반응 시기, 결핵 치료 기간, 치료 성공 여부, 치료 후 결핵 재발 여부 및 재발 시기를 의무기록을 이용하여 후향적으로 분석하였다. 신장 이식 후 결핵에 이환된 78예의 환자 중 26예(33.3%)는 폐결핵, 23예(29.5%)은 늑막결핵이었고, 5 예(6.4%)의 환자는 폐결핵과 늑막결핵이 동반되어 있었다. 이외에 속립결핵이 19예(24.4%), 장결핵이 2예였으며, 결핵성 복막염, 결핵성 뇌막염이 각각 1예였다. 폐결핵과 늑막결핵을 포함한 ‘폐결핵군’에서는 치료 중 거부반응, 치료 후

평균 이식신 생존기간, 치료 실패 및 치료 후 결핵이 재발할 때까지 기간이 리팜핀의 사용 여부에 따라 차이를 보이지 않았다. ‘폐외결핵군’에서는 리팜핀의 사용 여부에 따라, 치료 중 거부반응, 치료 후 평균 이식신 생존기간, 치료 실패에 차이를 보이지 않았다. ‘폐외결핵군’에서 치료 후 결핵이 재발할 때까지 기간은 리팜핀을 사용한 경우 87 ± 8 개월, 리팜핀을 사용하지 않은 경우 44 ± 7 개월로 리팜핀을 사용한 경우가 사용하지 않은 경우보다 늦게 재발하는 경향을 보였다.

결론적으로 신이식환자가 결핵에 이환되었을 경우, 약물의 상호작용을 충분히 고려하여 면역억제 치료를 하면 리팜핀은 이식신 생존기간에 영향을 미치지 않았다. 신이식환자가 폐외결핵에 이환된 경우에는 리팜핀이 결핵의 재발을 줄이는 경향이 있었으나, 폐결핵의 경우에는 좀더 많은 연구가 필요할 것으로 사료된다.

핵심되는 말: 결핵, 신장 이식, 리팜핀, 약물 상호작용