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Safety and Efficacy of a Quinolone-Based Regimen for Treatment of Tuberculosis in Renal Transplant Recipients

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ABSTRACT

Background. Rifampin (RFP) is a first-line antituberculosis drug, but it increases the risk of acute rejection (AR) in transplant recipients. This study evaluated whether quinolone (QNL) can replace RFP in renal transplant recipients with tuberculosis.

Methods. One hundred nine patients with active tuberculosis were included. Patients consisted of RFP (n = 91) and QNL (n = 18) groups based on the initial treatment regimen. Patients with RFP-associated adverse effects were subdivided into RFP-maintenance (RFP-M; n = 18) and QNL-conversion (QNL-C; n = 8) groups. Clinical outcomes were compared between groups.

Results. The incidence of AR was higher in the RFP group than in the QNL group (24.2% vs 5.6%). The QNL group showed significantly higher 10-year graft survival rates than the RFP group (88.1% vs 66.5%; $P = .022$). The QNL-C group showed significantly higher 10-year graft survival rates than the RFP-M group (87.5% vs 27.8%; $P = .011$). The rate of complete functional recovery after AR was higher in the QNL-C group than in the RFP-M group (50% vs 22.2%).

Conclusions. A QNL-based regimen may be safe and effective for treatment of tuberculosis and may lower the risk of graft failure in renal transplant recipients.

Tuberculosis (TB) is a serious opportunistic infection in renal transplant recipients. According to the Korean National Tuberculosis Association, the new TB case notification rate in Korea was 73 per 100,000 people in 2009, which is much higher than in Western countries.[1–3] The incidence among renal transplant recipients is also higher, ranging from 2.9% to 7.8%.[4–6] The first-line anti-TB drugs are isoniazid, rifampin (RFP), pyrazinamide, and ethambutol (or streptomycin), which generally result in >95% cure in uncomplicated TB infection.[7–9] However, because RFP is an inducer of the cytochrome P450 3A4 microsomal enzymes, it reduces blood levels of calcineurin inhibitors (CNIs).[10,11] As a result, the incidence of acute rejection (AR) and graft loss is increased in transplant patients using RFP.[1,3] Quinolones (QNLs) are commonly used for treatment of TB, especially in patients with multidrug-resistant TB or those with adverse effects from first-line drugs.[12,13] The successful treatment of TB with QNL in place of RFP was previously reported in renal transplant recipients.[14,15] However, there is no report comparing the outcomes between an RFP-based regimen and a QNL-based regimen. In the present study, clinical outcomes and adverse effects were compared between an RFP-based regimen and a QNL-based regimen, and the effect of QNL on allograft outcomes was evaluated in renal transplant recipients.

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METHODS

Between January 1984 and April 2009, 1,787 patients underwent renal transplantation at Seoul St Mary's Hospital and Daejeon St Mary's Hospital. Of these, 109 developed active TB during the study period. We retrospectively reviewed the medical records of these patients.

The RFP-based regimen was a daily oral regimen including RFP (450–600 mg), isoniazid (300–400 mg), ethambutol (800 mg), and pyrazinamide (1,000–1,500 mg). The QNL-based regimen included levofloxacin (500–1,000 mg) instead of RFP. Levofloxacin was chosen because of a long-term safety profile.[16] Treatment was continued for at least 6 months using the RFP-based regimen and at least 12 months using the QNL-based regimen, because regimens not including RFP should be continued for 12–18 months.[3,15] In the RFP-based regimen, the dose of CNI was increased 2–5-fold to maintain stable trough levels.[17–19]

According to the initial treatment regimen, patients consisted of an RFP-based group (n = 91) and a QNL-based group (n = 18). Each group was further divided into an AR group and a non-AR group depending on the development of AR during anti-TB treatment. In addition, patients with RFP-associated adverse effects were subdivided into 2 groups: patients who developed AR but continued RFP (RFP-maintenance [RFP-M]; n = 18) or those who replaced RFP with QNL (QNL-conversion [QNL-C]; n = 8). Clinical outcomes were compared the between RFP and QNL groups and between the RFP-M and QNL-C groups. The study was approved by our Institutional Review Board (KC11RISI0117). Continuous data are presented as mean ± SD and were compared by Student *t* test or paired *t* test. Statistical analysis was performed using SPSS software. Categoric data were compared by chi-square tests or Fisher exact tests. Kaplan-Meier curves and log-rank tests were used to describe and compare the survival rates for allografts. A *P* value of <.05 was taken to indicate significance.

RESULTS

Patient characteristics did not differ between the RFP and QNL groups, except that the average duration of anti-TB treatment was significantly longer in the QNL group than in the RFP group (Table 1). The incidence of AR during anti-TB treatment was 4 times higher in the RFP group than in the QNL group (24.2% vs 5.6%). The overall graft survival rates for the QNL group were significantly higher than those for the RFP group (94.4% at 5 years and 88.1% at 10 years vs 79.8% at 5 years and 66.5% at 10 years; $P = .022$). Graft failure developed in 43 patients (47.3%) in the RFP group and in 2 patients (11.1%) in the QNL group. Eight cases of graft failure (18.6%) in the RFP group were due to AR during anti-TB treatment.

RFP was replaced by QNL in 4 patients in the AR group and in 4 patients in the non-AR group because of other adverse effects: hepatotoxicity (n = 2); arthralgia and decreased visual acuity (n = 1); and RFP resistance (n = 1). The graft survival rates for the QNL-C group were significantly higher than those for the RFP-M group (87.5% at both 5 years and 10 years vs 50.0% at 5 years and 27.8% at 10 years; $P = .011$). In the RFP-M group, graft function deteriorated after AR in 10 patients (55.6%), and complete functional recovery, defined as the antirejection treatment recovering graft function to within 10% of the baseline value, was noted in only 4 patients (22.2%). In contrast, in the QNL-C group, graft function deteriorated in 1 patient (25%) and complete functional recovery was noted in 2 patients (50%).

Table 1. Comparison of Patient Characteristics Between the RFP and QNL Groups

	RFP (n = 91)	QNL (n = 18)	*P* Value
Age, y	41 ± 11	43 ± 12	.490
Female sex, n (%)	30 (33.0)	6 (33.3)	.976
Pre-Tx Diabetes, n (%)	31 (34.1)	5 (27.8)	.604
Pre-Tx Dialysis modality, n (%), HD:PD:none	83 (91.2):6 (6.6):2 (2.2)	15 (83.3):3 (16.7):0 (0)	.310
Deceased donor, n (%)	15 (16.5)	4 (22.2)	.514
Donor age, y	38 ± 13	40 ± 12	.517
Donor sex female, n (%)	32 (35.2)	7 (38.9)	.763
HLA mismatch no.	3.1 ± 1.4	4.7 ± 1.5	.057
Retransplant, n (%)	7 (7.7)	1 (5.6)	1.000
Pre-Tx transfusion, n (%)	76 (83.5)	14 (77.8)	.514
Pre-Tx maximum PRA, %	0 ± 0	6.7 ± 11.5	.629
Current PRA, %	8.0 ± 16.0	6.7 ± 11.5	.948
Serum creatinine, mg/dL	2.0 ± 1.4	1.6 ± 0.8	.283
Months from Tx to Dx of TB	50 ± 56	55 ± 61	.728
Prior history of TB, n (%)	2 (2.2)	1 (5.6)	.421
Site of infection, n (%)			
Pulmonary	45 (49.5)	11 (61.1)	
Extrapulmonary	31 (34.1)	7 (38.9)	.053
Combined	15 (16.5)	0 (0)	
Months on anti-TB medication	10 ± 5	12 ± 1	<.001
Follow-up years after Dx of TB	8 ± 6	8 ± 4	.808

Abbreviations: RFP, rifampin; QNL, quinolone; Tx, transplantation; HD, hemodialysis; PD, peritoneal dialysis; PRA, panel reactive antibody; Dx, diagnosis; TB, tuberculosis.