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Renal Transplantation in Patients With Tuberculosis: A Single-center Experience From an Endemic Region

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Background. Despite being a common infection in end-stage kidney disease patients, there are no evidence-based guidelines to suggest the ideal time of transplantation in patients on antitubercular therapy (ATT). This study aimed to examine the outcome of transplantation in patients while on ATT compared with those without tuberculosis (TB). **Methods.** This was a retrospective study. Renal transplant recipients transplanted while on ATT were compared with a 1:1 matched group (for age, sex, diabetic status, and type of induction agent) of patients without TB at the time of transplant. Patient outcomes included relapse of TB and graft and patient survival. **Results.** There were 71 patients in each group. The mean duration for which ATT was given pretransplant was 3.8 ± 2.47 mo. The average total duration of ATT received was 12.27 ± 1.25 mo. Mortality in both the groups was similar (8.4% in the TB group versus 4.5% in the non-TB group; $P = 0.49$). None of the surviving patients had recurrence of TB during the follow-up. Death-censored graft survival (98.5% in the TB group versus 97% in the non-TB group; $P = 1$) and biopsy-proven acute rejection rates (9.86% in the TB group versus 8.45% in the non-TB group; $P = 1$) were also similar in both the groups. **Conclusions.** Successful transplantation in patients with end-stage kidney disease on ATT is possible without any deleterious effect on patient and graft survival and no risk of disease recurrence. Multicentric prospective studies are needed.

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Tuberculosis (TB) is the 13th leading cause of death and the second leading infectious killer after COVID-19 (above HIV/AIDS). In 2020, an estimated 10 million people developed TB worldwide. India contributes to 27% of the global burden of TB.[1] Patients with end-stage kidney disease (ESKD) on dialysis are 6–25 times more likely to develop TB than the general population because of impaired cellular immunity. In India, the incidence of TB is between 8.7% and 13.6% in ESKD patients and 12.3%–14% in renal transplant recipients.[2-4] Treatment of this group of patients is difficult considering the drug interactions and higher incidences of side effects related to antitubercular therapy (ATT). The treatment duration in these patients is also not defined clearly, and they might need longer therapy.

Most of the recent research and guidelines address the management of latent TB in renal transplant candidates.[5-7] At present, there are no evidence-based guidelines to suggest the ideal time of transplantation in patients on ATT. Most of the published guidelines suggest fully treating active TB before transplantation with the possible exception of emergency transplantation with very low quality of evidence (level D) to support this practice.[8,9] Even Kidney disease: improving Global Outcomes 2020 guidelines suggest complete treatment of active TB as per the World Health Organization or advise to follow local recommendations (grade 2C recommendation).[10] This delays the transplantation and increases the chance of dialysis-related morbidity and mortality. This is even more important in patients waiting on the deceased donation list

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who may lose a chance of getting a kidney. Limited access to quality dialysis in developing countries makes this situation even worse. Due to these limitations and TB being an endemic infection in India, most Indian centers accept their patients with ESKD for a kidney transplant after a minimum of 2 mo of intensive treatment with 4 drugs after ensuring clinical and radiological remission. Patients complete the rest of the ATT course after transplant. A recently published South Asian expert group opinion on the management of TB in solid organ transplantation suggests transplantation after completion of intensive phase if early transplant is desired.[11] However, there is little evidence to support this strategy in the current literature. Lee et al[12] have published their experience of successful transplantation in 9 patients with liver failure and concurrent TB. Patients were on modified ATT (less hepatotoxic). No patient had a relapse of TB with a median follow-up of 926 d with 1 patient on rifabutin developing acute rejection. Sun[13] reviewed 34 published case reports of patients undergoing transplantation. Although follow-up data were unavailable in 6 patients, in patients with available data, rejections were significantly more in patients on a rifampicin-containing regimen compared with those on a rifampicin-free regimen (83.3% versus 13.3%; P = 0.006). However, mortality did not differ between those treated with or without rifampicin.

So, we retrospectively reviewed our patients who got transplanted while on ATT and compared them with those without TB at the time of transplantation.

PATIENTS AND METHODS

This was a retrospective study. We screened all the renal transplant recipients from 2014 to 2020 to find patients who were on ATT at the time of transplantation. Demographic data, comorbidities, the type of induction agent used in transplant, indication of starting ATT, and the type and duration of ATT in pretransplant and posttransplant period were collected. Patient outcomes studied included relapse of TB and graft and patient survival. Data were collected from our transplant database that is maintained prospectively.

We compared these patients with those who were not on ATT at the time of transplant. The matched comparison group was chosen with 1:1 matching for age, sex, diabetic status, and type of induction agent.

TB was diagnosed and defined as per the standard case definition provided in the World Health Organization guidelines.[14] Patients without microbiological confirmation were not excluded from the study. At our center, ESKD patients with TB received 4-drug ATT with isoniazid 5 mg/kg, rifampicin 10 mg/kg, ethambutol 15 mg/kg thrice weekly postdialysis, pyrazinamide 25 mg/kg thrice weekly postdialysis (renal adjusted doses) for 2–3 mo followed by 2- to 3-drug ATT in continuation phase, which is continued for a total of 9–12 mo, sometimes up to 18 mo in cases of disseminated, skeletal, and Central Nervous System TB. Posttransplant patients receive rifampicin-sparing ATT. Patients of the present study received standard triple-drug maintenance immunosuppression with tacrolimus, mycophenolate mofetil, and steroids in the posttransplant period. All the patients were followed up for a minimum of 1 y duration after completion of ATT.

Statistical analysis for this study was performed using SAS software, version 2021 (SAS Institute, Inc, Cary, NC). Data are reported as mean ± SD. Continuous variables were compared using the unpaired t test, Mann–Whitney U test, and ANOVA test, whereas categorical values were compared using the chi-square or Fisher exact test. Multivariable regression analysis was performed to detect independent predictors of outcomes. A P value of <0.05 was considered significant. The study was completed in accordance with the 1964 Helsinki Declaration and its later amendments.

RESULTS

Of the 1729 patients who underwent kidney transplants during the study period, 71 (4.1%) were on ATT at the time of transplantation. A comparison group of 71 patients without a history of TB at the time of transplant was chosen. The mean follow-up duration was 49.38 ± 27.8 mo for patients in the TB group, whereas it was 50.95 ± 25.9 mo for those in the non-TB group. Eleven patients were lost to follow-up (6 in the TB group and 5 in the non-TB group). Table 1 shows the demographic details of the patients in each group, whereas Table 2 shows the indication for starting ATT. Mean dialysis vintage was significantly higher in the TB group. Also, a

TABLE 1.
Demographic details of patients

Baseline characteristics	With tuberculosis (n = 71)	Without tuberculosis (n = 71)	P
Age, mean ± SD, y	39.78 ± 11.9	40.15 ± 11.7	0.85
Sex, M:F, n	49:22	49:22	1
Dialysis vintage, mean ± SD, mo	7.05 ± 7.5	4.56 ± 5	0.0214[a]
HLA mismatch (–/6), mean ± SD	3.49 ± 1.26	3.5 ± 1.56	0.96
History of previous immunosuppression, n	16	6	0.0351[a]
Diabetes, n	15	15	1
CAD, n	6	5	1
HTN, n	67	65	0.74
HCV, n	6	1	0.11
HBV, n	3	0	0.24
HIV, n	0	0	1
Induction, n	53	52	1
IL2, n	28	26	0.86
ATG, n	25	26	1

[a] Significant.
ATG, antithymocyte globulin; CAD, coronary artery disease; HBV, hepatitis B virus; HCV, hepatitis C virus; HTN, hypertension; IL2, interleukin-2; M:F, male:female.

TABLE 2.
Indications for antitubercular therapy

Indications	n
TB lymphadenitis	44
TB pleural effusion	11
TB pleural + pericardial effusion	2
PUO	3
Abdominal TB	4
Pulmonary TB	4
TB arthritis/osteomyelitis	2
Submandibular abscess	1

PUO, pyrexia of unknown origin; TB, tuberculosis.

significantly higher number of patients in the TB group had a history of prior immunosuppression.

Treatment Details of ATT

The mean duration for which ATT was given was 3.8 ± 2.47 mo pretransplant and 8.66 ± 2.73 mo posttransplant. The average total duration for which ATT received was 12.27 ± 1.25 mo.

Pretransplant ATT details were not available for 4 patients. All the remaining 67 patients were started on a 4-drug ATT regimen of isoniazid, rifampicin, pyrazinamide, and ethambutol. Of these, ATT was modified in 16 patients because of side effects (uncontrolled hypertension in 8, hepatitis in 6, optic neuritis in 1, and psychosis in 3 patients).

All continuation phase posttransplant was rifampicin-free with either 2 or 3 drugs, with different combinations of isoniazid, ethambutol, pyrazinamide, and fluoroquinolone.

Posttransplant ATT details for patients are as follows: 13 patients were on a 2-drug ATT regimen, 40 patients on 3-drug ATT regimen, 14 patients on 4-drug ATT regimen (which changed to 3 or 2 drugs after 1–2 mo), and for 1 patient, data were unavailable.

TABLE 3.
Outcome of patients

Outcome parameter	With tuberculosis (n = 71)	Without tuberculosis (n = 71)	*P*
Mean creatinine at last follow-up, mean ± SD, mg/dL	1.45 ± 0.97	1.3 ± 0.66	0.28
Mortality, n (%)	6 (8.45)	3 (4.5)	0.49
Death-censored graft failure, n (%)	1 (1.5)	2 (3)	1
Biopsy-proven acute rejection, n (%)	7 (9.86)	6 (8.45)	1

Outcome

Table 3 shows the outcomes of patients in the 2 groups.

There were 6 mortalities in the TB groups. The cause of death was cytomegalovirus, COVID infection, and cardiac arrest in 1 patient each and bacterial sepsis in 2 patients, whereas the cause of death was not clear for 1 patient (who was found dead at home).

Of these 6 patients, 3 died while on ATT. The immediate cause of death was cytomegalovirus colitis–related complication in 1patient and bacterial septic shock in 2 patients. None of the remaining surviving patients had a recurrence of TB during the follow-up. There was no difference in patient survival between the groups according to the Kaplan–Meier analysis (Figure 1).

DISCUSSION

Transplantation in patients with TB undergoing treatment is a contentious issue. The European guidelines suggest completing ATT before transplantation except in cases of emergency transplantations such as heart, liver, and lung transplantation, although the level of evidence for this suggestion is very poor.[8] The present study looked at the outcome of transplantation in patients with TB while on ATT vis-à-vis those without TB at the time of transplant. This is probably the first such large study on this issue.

Most of our patients had extrapulmonary TB, with TB lymphadenitis being the most common presentation. Only 4 (5%) patients had pulmonary TB. Compared with the general population, extrapulmonary TB is more common in patients on hemodialysis.[15,16]

All the patients except 3 in the present study had completed the intensive phase of treatment before going ahead with the

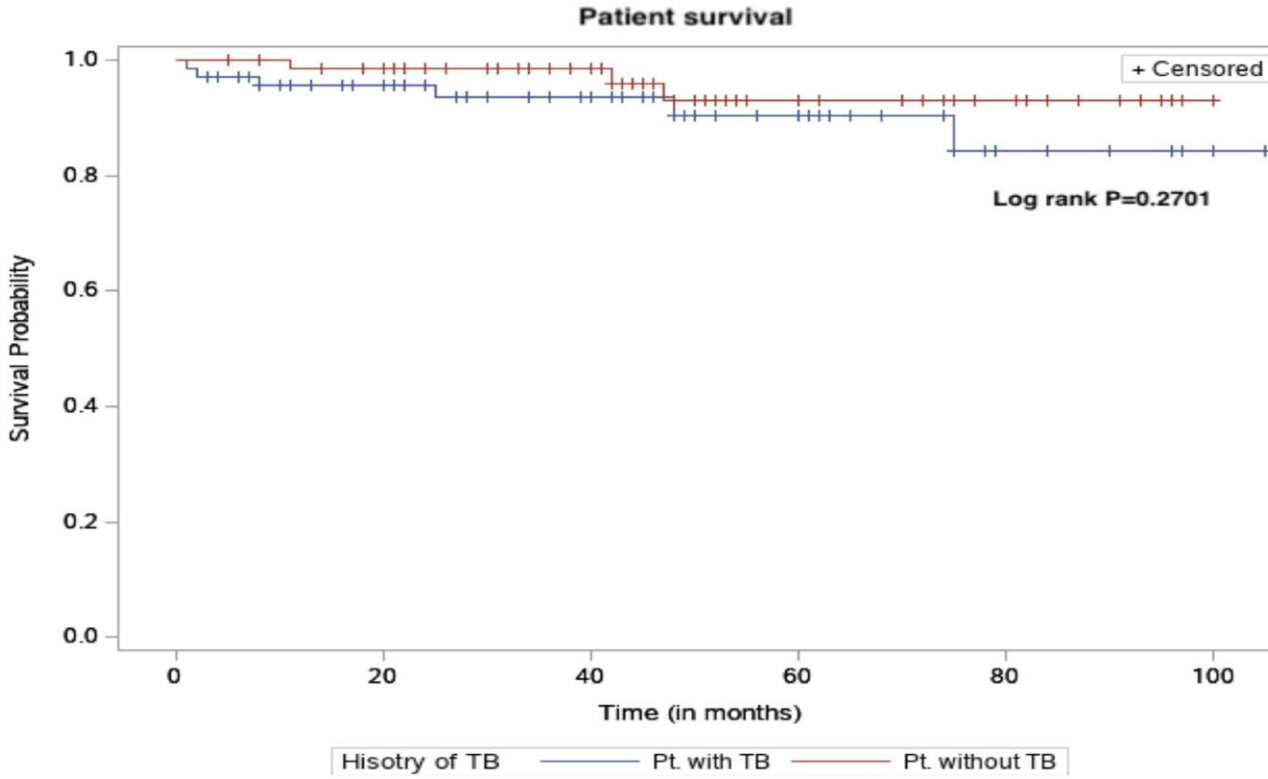

FIGURE 1. Kaplan–Meier curve for patient survival. Pt., patient; TB, tuberculosis.

transplant. The mean pretransplant ATT duration was 3.8 mo. Only 3 patients underwent transplant at <2 mo of treatment. None of the patients had a recurrence of the disease in the present study. In a study by Vachharajani et al,[4] 4 patients underwent transplantation while on ATT, 2 after 3 mo of ATT, and 2 after 6 mo of ATT. None had reactivation.[4]

The ideal duration of therapy needed is controversial. The mean duration of treatment in the present study was 12.2 mo. Considering the rifampicin-free continuation phase, in immunocompromised patients, a longer maintenance phase therapy with 2–3 drugs is needed.[9]

Shorter courses can increase mortality and relapse rates. A Spanish study observed that administration of treatment for <9 mo was associated with greater chances of rejection and mortality.[17] Another study observed that the only factor that was significantly associated with greater recurrence of TB was the duration of treatment. No recurrence was observed in the patients who received >12 mo of treatment, irrespective of whether the treatment regimen included rifampicin.[18]

The mean posttransplant follow-up duration of patients who received ATT in the current study was 49.38 mo. Total mortality in this group was 8.45% (6/71). Both mortality and death-censored graft failure were not significantly different from patients who had no history of TB. Although the difference did not reach statistical significance, it is not possible to rule out a type II error associated, as the study is underpowered to detect a difference with observed magnitude. None of the deaths was directly attributable to TB. In 1 case, the cause of death was unclear. This is in contrast to the study from South India, where mortality in TB in ESKD was high at 18.3%.[15] Studies from other countries also have shown higher mortality in patients with TB undergoing dialysis.[16,19] Chou et al[16] compared their patients with the nondialysis population with TB and found that mortality due to TB was similar in both the groups (1.7% versus 1.9%), and it was the mortality in the non-TB group that was significantly higher in the dialysis population (25.6% versus 11.1%). This emphasizes the necessity of early treatment of uremia (transplantation) along with treatment of TB.

Graft outcome was similar in both groups in terms of graft function and death-censored graft failure both in univariate and in multivariable analysis. The omission of rifampicin in posttransplant ATT makes immunosuppression management easier, leading to a lesser effect on graft outcome.

A few things should be kept in mind while treating TB. *Mycobacterium tuberculosis* is a slow-growing bacillus, and some bacteria will remain in dormant stage requiring longer therapy. Pyrazinamide and rifampicin are more important in that matter. When rifampicin cannot be used, levofloxacin can be used. The use of rifampicin-sparing ATT is controversial. Studies in populations other than solid organ transplant recipients have shown an increased risk of TB recurrence and high TB resistance rates when rifampicin-sparing regimens are used.[20] In transplant recipients, rifampicin-including regimens have increased the frequency of rejection and mortality.[21,22] Use of rifampicin in these patients would lead to a significant reduction in calcineurin inhibitors and mammalian target of rapamycin inhibitors levels, and their dose needs to be increased by 3–5 times, which is sometimes unpredictable, thus increasing the risk of acute rejections in up to 30% of cases and graft loss in up to 20%.[23] Although some series have demonstrated that these drugs may be safe with rigorous control of immunosuppressor levels,[24-26] current approach of completing rifampicin-based intensive phase before transplant and continuing rifampicin-free 2- to 3-drug therapy posttransplant gives the advantage of bactericidal effect of rifampicin with avoiding risks related to immunosuppression interactions in posttransplant phase.

Even though the current study throws some light on the appropriate time of transplantation in patients on ATT, it has a few limitations. First, this is a retrospective study and hence has limitations inherent to it. Second, the sample size was small. Third, there was no uniformity in the type of ATT used and the duration of therapy. Despite these limitations, the present study is important as it shows the feasibility of transplantation in patients while receiving ATT with good patient and graft outcomes without major risk of recurrence.

To conclude, we could successfully perform transplantation in patients with ESKD while on ATT without any deleterious effect on patient and graft survival and with no risk of disease recurrence. This supports the current practice of performing transplantation in patients after completion of an intensive phase, which is being followed in most centers of India. Further multicentric studies are required in this direction.

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